ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Vokanamet 50 mg/850 mg film-coated tablets
Vokanamet 50 mg/1,000 mg film-coated tablets
Vokanamet 150 mg/850 mg film-coated tablets
Vokanamet 150 mg/1,000 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Vokanamet 50 mg/850 mg film-coated tablets

Each tablet contains canagliflozin hemihydrate, equivalent to 50 mg of canagliflozin, and 850 mg of metformin hydrochloride.

Vokanamet 50 mg/1,000 mg film-coated tablets

Each tablet contains canagliflozin hemihydrate, equivalent to 50 mg of canagliflozin, and 1,000 mg of metformin hydrochloride.

Vokanamet 150 mg/850 mg film-coated tablets

Each tablet contains canagliflozin hemihydrate, equivalent to 150 mg of canagliflozin, and 850 mg of metformin hydrochloride.

Vokanamet 150 mg/1,000 mg film-coated tablets

Each tablet contains canagliflozin hemihydrate, equivalent to 150 mg of canagliflozin, and 1,000 mg of metformin hydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Vokanamet 50 mg/850 mg film-coated tablets

The tablet is pink, capsule-shaped, 20 mm in length, film-coated, and debossed with “CM” on one side and “358” on the other side.

Vokanamet 50 mg/1,000 mg film-coated tablets

The tablet is beige, capsule-shaped, 21 mm in length, film-coated, and debossed with “CM” on one side and “551” on the other side.

Vokanamet 150 mg/850 mg film-coated tablets

The tablet is light yellow, capsule-shaped, 21 mm in length, film-coated, and debossed with “CM” on one side and “418” on the other side.

Vokanamet 150 mg/1,000 mg film-coated tablets

The tablet is purple, capsule-shaped, 22 mm in length, film-coated, and debossed with “CM” on one side and “611” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vokanamet is indicated in adults with type 2 diabetes mellitus as an adjunct to diet and exercise:

- in patients insufficiently controlled on their maximally tolerated doses of metformin alone
- in combination with other medicinal products for the treatment of diabetes, in patients insufficiently controlled with metformin and these medicinal products
- in patients already being treated with the combination of canagliflozin and metformin as separate tablets.

For study results with respect to combination of therapies, effects on glycaemic control and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1.

4.2 Posology and method of administration

Posology

Adults with normal renal function (estimated glomerular filtration rate [eGFR] ≥ 90 mL/min/1.73 m^2)

The dose of glucose-lowering therapy with Vokanamet should be individualised on the basis of the patient's current regimen, effectiveness, and tolerability, using the recommended daily dose of 100 mg or 300 mg canagliflozin and not exceeding the maximum recommended daily dose of metformin orally.

For patients inadequately controlled on maximal tolerated dose of metformin

For patients not adequately controlled on metformin, the recommended starting dose of Vokanamet should provide canagliflozin dosed at 50 mg twice daily plus the dose of metformin already being taken or the nearest therapeutically appropriate dose. For patients who are tolerating a Vokanamet dose containing canagliflozin 50 mg who need tighter glycaemic control, the dose can be increased to Vokanamet containing 150 mg canagliflozin twice daily (see below and section 4.4).

For patients switching from separate tablets of canagliflozin and metformin

For patients switching from separate tablets of canagliflozin and metformin, Vokanamet should be initiated at the same total daily dose of canagliflozin and metformin already being taken or the nearest therapeutically appropriate dose of metformin.

Dose titration with canagliflozin (added to the optimal dose of metformin) should be considered before the patient is switched to Vokanamet.

In patients tolerating Vokanamet containing canagliflozin 50 mg who need tighter glycaemic control, increasing the dose to Vokanamet containing canagliflozin 150 mg may be considered.

Care should be taken when increasing the dose of Vokanamet containing 50 mg of canagliflozin to 150 mg of canagliflozin in patients ≥ 75 years of age, patients with known cardiovascular disease, or other patients for whom the initial canagliflozin-induced diuresis poses a risk (see section 4.4). In patients with evidence of volume depletion, correcting this condition prior to initiation of Vokanamet is recommended (see section 4.4).

When Vokanamet is used as add-on therapy with insulin or an insulin secretagogue (e.g., a sulphonylurea), a lower dose of insulin or the insulin secretagogue may be considered to reduce the risk of hypoglycaemia (see sections 4.5 and 4.8).

Special populations

Elderly
Because metformin is eliminated in part by the kidney and elderly patients are more likely to have decreased renal function, Vokanamet should be used with caution as age increases. Regular assessment of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in elderly patients. The risk of volume depletion associated with canagliflozin should be taken into account (see sections 4.3 and 4.4).

Renal impairment
Vokanamet is contraindicated in patients with severe renal failure (eGFR < 30 mL/min) (see section 4.3).

An eGFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at increased risk of further progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

The maximum daily dose of metformin should preferably be divided into 2-3 daily doses.

Risk factors that may increase the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of metformin in patients with eGFR < 60 mL/min/1.73 m^2.

If no adequate strength of Vokanamet is available, individual monocomponents should be used instead of the fixed dose combination (see table 1).

Table 1: Dose adjustment recommendations

eGFR mL/min/1.73 m^2	Metformin	Canagliflozin
60-89	Maximum daily dose is 3,000 mg Dose reduction may be considered in relation to declining renal function.	Maximum total daily dose is 300 mg.
45-59	Maximum daily dose is 2,000 mg The starting dose is at most half of the maximum dose.	Canagliflozin should not be initiated. Patients tolerating canagliflozin can continue use at a maximum total daily dose of 100 mg.
30-44	Maximum daily dose is 1,000 mg. The starting dose is at most half of the maximum dose.	Canagliflozin should not be used.
< 30	Metformin is contraindicated.	Canagliflozin has not been studied in severe renal impairment.

Hepatic impairment
Vokanamet is contraindicated in patients with hepatic impairment due to the active substance metformin (see sections 4.3 and 5.2). There is no clinical experience with Vokanamet in patients with hepatic impariment.

Paediatric population

The safety and efficacy of Vokanamet in children under 18 years of age have not been established. No data are available.

Method of administration

For oral use

Vokanamet should be taken orally twice daily with meals to reduce the gastrointestinal undesirable effects associated with metformin. Tablets are to be swallowed whole.

If a dose is missed, it should be taken as soon as the patient remembers unless it is time for the next dose in which case patients should skip the missed dose and take the medicinal product at the next regularly scheduled time.

4.3 Contraindications

- Hypersensitivity to the active substances or any of the excipients listed in section 6.1;
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis);
- Diabetic pre-coma;
- Severe renal failure (eGFR < 30 mL/min/1.73 m^2) (see sections 4.2 and 4.4);
- Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock (see section 4.4);
- Acute or chronic disease which may cause tissue hypoxia such as: cardiac or respiratory failure, recent myocardial infarction, shock;
- Hepatic impairment, acute alcohol intoxication, alcoholism (see sections 4.2 and 4.5).

4.4 Special warnings and precautions for use

Lactic acidosis

Lactic acidosis, a very rare but serious metabolic complication, most often occurs at acute worsening of renal function or cardiorespiratory illness or sepsis. Metformin accumulation occurs at acute worsening of renal function and increases the risk of lactic acidosis.

In case of dehydration (severe diarrhoea or vomiting, fever or reduced fluid intake), Vokanamet should be temporarily discontinued and contact with a healthcare professional is recommended.

Medicinal products that can acutely impair renal function (such as antihypertensives, diuretics and non-steroidal anti-inflammatory drugs [NSAIDs]) should be initiated with caution in Vokanamet-treated patients. Other risk factors for lactic acidosis are excessive alcohol intake, hepatic insufficiency, inadequately controlled diabetes, ketosis, prolonged fasting and any conditions associated with hypoxia, as well as concomitant use of medicinal products that may cause lactic acidosis (see sections 4.3 and 4.5).

Patients and/or care-givers should be informed of the risk of lactic acidosis. Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain, muscle cramps, asthenia and hypothermia followed by coma. In case of suspected symptoms, the patient should stop taking Vokanamet and seek immediate medical attention. Diagnostic laboratory findings are decreased blood pH (< 7.35), increased plasma lactate levels (> 5 mmol/L) and an increased anion gap and lactate/pyruvate ratio.

The risk of lactic acidosis must be considered in the event of non-specific signs such as muscle cramps with digestive disorders as abdominal pain and severe asthenia.

Patients with known or suspected mitochondrial diseases
In patients with known mitochondrial diseases such as Mitochondrial Encephalopathy with Lactic Acidosis, and Stroke-like episodes (MELAS) syndrome and Maternally inherited diabetes and deafness (MIDD), metformin is not recommended due to the risk of lactic acidosis exacerbation and neurologic complications which may lead to worsening of the disease.

In case of signs and symptoms suggestive of MELAS syndrome or MIDD after the intake of metformin, treatment with metformin should be withdrawn immediately and prompt diagnostic evaluation should be performed.

Renal function

Decreased renal function in elderly patients is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired; for example, when initiating antihypertensive or diuretic therapy and when starting treatment with a NSAID.

The efficacy of canagliflozin for glycaemic control is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment (see section 4.2).

In patients with an eGFR < 60 mL/min/1.73 m^2 or CrCl < 60 mL/min, a higher incidence of adverse reactions associated with volume depletion (e.g., postural dizziness, orthostatic hypotension, hypotension) was reported, particularly with the 300 mg dose. In addition, in such patients more events of elevated potassium and greater increases in serum creatinine and blood urea nitrogen (BUN) were reported (see section 4.8).

Therefore, the canagliflozin dose should be limited to 100 mg daily in patients with eGFR < 60 mL/min/1.73 m^2 or CrCl < 60 mL/min and canagliflozin should not be used for the purpose of glycaemic control in patients with an eGFR persistently < 45 mL/min/1.73 m^2 or CrCl < 45 mL/min (see section 4.2).

Administration of iodinated contrast agent

Intravascular administration of iodinated contrast agents may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Vokanamet should be discontinued prior to, or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable (see sections 4.2 and 4.5).

Surgery

As Vokanamet contains metformin, Vokanamet must be discontinued at the time of surgery under general, spinal, or epidural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and provided that renal function has been re-evaluated and found to be stable.

Vitamin B_{12} decrease/deficiency

Metformin may reduce vitamin B_{12} serum levels. The risk of low vitamin B_{12} levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B_{12} deficiency. In case of suspicion of vitamin B_{12} deficiency (such as anaemia or neuropathy), vitamin B_{12} serum levels should be monitored. Periodic vitamin B_{12} monitoring could be necessary in patients with risk factors for vitamin B_{12} deficiency. Metformin therapy should be continued for as long as it is tolerated and not contra-indicated and appropriate corrective treatment for vitamin B_{12} deficiency provided in line with current clinical guidelines.

Use in patients at risk for adverse reactions related to volume depletion

Due to its mechanism of action, canagliflozin, by increasing urinary glucose excretion (UGE), induces an osmotic diuresis, which may reduce intravascular volume and decrease blood pressure (see section 5.1). In controlled clinical studies of canagliflozin, increases in adverse reactions related to volume depletion (e.g., postural dizziness, orthostatic hypotension, or hypotension) were seen more commonly with a daily dose of 300 mg canaliflozin and occurred most frequently in the first three months (see section 4.8).

Caution should be exercised in patients for whom a canagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients with an

eGFR < 60 mL/min/1.73 m^2, patients on anti-hypertensive therapy with a history of hypotension, patients on diuretics, or elderly patients (≥ 65 years of age) (see sections 4.2 and 4.8).

Due to volume depletion, generally small mean decreases in eGFR were seen within the first 6 weeks of treatment initiation with canagliflozin. In patients susceptible to greater reductions in intravascular volume as described above, larger decreases in eGFR (> 30%) were sometimes seen, which subsequently improved, and infrequently required interruption of treatment with canagliflozin (see section 4.8).

Patients should be advised to report symptoms of volume depletion. Canagliflozin is not recommended for use in patients receiving loop diuretics (see section 4.5) or who are volume depleted, e.g., due to acute illness (such as gastrointestinal illness).

For patients receiving Vokanamet, in case of intercurrent conditions that may lead to volume depletion (such as a gastrointestinal illness), careful monitoring of volume status (e.g., physical examination, blood pressure measurements, laboratory tests including renal function tests), and serum electrolytes is recommended. Temporary interruption of treatment with Vokanamet may be considered for patients who develop volume depletion while on Vokanamet therapy until the condition is corrected. If interrupted, consideration should be given to more frequent glucose monitoring.

Diabetic ketoacidosis

Rare cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases, have been reported in patients treated with SGLT2 inhibitors, including canagliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/L (250 mg/dL). It is not known if DKA is more likely to occur with higher doses of canagliflozin. Risk of DKA appears to be higher in patients with moderately to severely decreased renal function who require insulin.

The risk of diabetic ketoacidosis must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level.

In patients where DKA is suspected or diagnosed, treatment with Vokanamet should be discontinued immediately.

Treatment should be interrupted in patients who are hospitalised for acute serious medical illnesses. Withhold Vokanamet, if possible, for an appropriate period of time (days) prior to major surgery, including abdominal and bariatric, or any other invasive procedures associated with prolonged fasting. Monitoring for serum ketones is recommended. Consider alternative anti-hyperglycaemic therapy, including insulin.

Measurement of blood ketone levels is preferred to urine. Treatment with Vokanamet may be restarted when the ketone values are normal and the patient's condition has stabilised.

Before initiating Vokanamet, factors in the patient history that may predispose to ketoacidosis should be considered.

Diabetic ketoacidosis may be prolonged after discontinuation of Vokanamet in some patients, i.e. it may last longer than expected from the plasma half-life of canagliflozin (see section 5.2). Prolonged glucosuria has been observed along with persistent DKA. Canagliflozin-independent factors might be involved in prolonged periods of DKA. Insulin deficiency may contribute to prolonged diabetic ketoacidosis and has to be corrected when verified.

Patients who may be at higher risk of DKA include patients with a low beta-cell function reserve (e.g., type 2 diabetes patients with low C-peptide or latent autoimmune diabetes in adults (LADA) or

patients with a history of pancreatitis), patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse. SGLT2 inhibitors should be used with caution in these patients.

Restarting SGLT2 inhibitor treatment in patients with previous DKA while on SGLT2 inhibitor treatment is not recommended unless another clear precipitating factor is identified and resolved.

The safety and efficacy of canagliflozin in patients with type 1 diabetes have not been established and Vokanamet should not be used for treatment of patients with type 1 diabetes. Limited data from clinical studies suggest that DKA occurs with common frequency when patients with type 1 diabetes are treated with SGLT2 inhibitors.

Lower limb amputations

In long-term clinical studies of canagliflozin in patients with type 2 diabetes with established cardiovascular disease (CVD) or at least 2 risk factors for CVD, canagliflozin was associated with an increased risk of lower limb amputation *versus* placebo (0.63 vs 0.34 events per 100 patient-years, respectively), and this increase occurred primarily in the toe and midfoot (see section 4.8). In a long-term clinical study in patients with type 2 diabetes and diabetic kidney disease, no difference in lower limb amputation risk was observed in patients treated with canagliflozin 100 mg relative to placebo. In this study precautionary measures as outlined below were applied. As an underlying mechanism has not been established, risk factors, apart from general risk factors, for amputation are unknown.

Before initiating Vokanamet, consider factors in the patient history that may increase the risk for amputation. As precautionary measures, consideration should be given to carefully monitoring patients with a higher risk for amputation events and counselling patients about the importance of routine preventative foot care and maintaining adequate hydration. Consideration may also be given to stopping treatment with Vokanamet in patients who develop events which may precede amputation such as lower-extremity skin ulcer, infection, osteomyelitis or gangrene.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Post-marketing cases of necrotising fasciitis of the perineum, (also known as Fournier's gangrene), have been reported in female and male patients taking SGLT2 inhibitors. This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.

Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, Vokanamet should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Elevated haematocrit

Haematocrit increase was observed with canagliflozin treatment (see section 4.8); therefore, careful monitoring in patients with already elevated haematocrit is warranted.

Elderly

Elderly patients may be at a greater risk for volume depletion, are more likely to be treated with diuretics, and to have impaired renal function. In patients ≥ 75 years of age, a higher incidence of adverse reactions associated with volume depletion (e.g., postural dizziness, orthostatic hypotension, hypotension) was reported with canagliflozin therapy. In addition, in such patients greater decreases in eGFR were reported (see sections 4.2 and 4.8).

Genital mycotic infections

Consistent with the mechanism of sodium glucose co-transporter 2 (SGLT2) inhibition with increased UGE, vulvovaginal candidiasis in females and balanitis or balanoposthitis in males were reported in clinical studies with canagliflozin (see section 4.8). Male and female patients with a history of genital mycotic infections were more likely to develop an infection. Balanitis or balanoposthitis occurred primarily in uncircumcised male patients which in some instances resulted in phimosis and/or circumcision. The majority of genital mycotic infections were treated with topical antifungal treatments, either prescribed by a healthcare professional or self-treated while continuing therapy with Vokanamet.

Urinary tract infections

Post-marketing cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with canagliflozin, frequently leading to treatment interruption. Temporary interruption of canagliflozin should be considered in patients with complicated urinary tract infections.

Cardiac failure

Experience in New York Heart Association (NYHA) class III is limited, and there is no experience in clinical studies with canagliflozin in NYHA class IV.

Urine laboratory assessments

Due to canagliflozin's mechanism of action, patients taking Vokanamet will test positive for glucose in their urine.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic drug interaction studies with Vokanamet have not been performed; however, such studies have been conducted with the individual active substances (canagliflozin and metformin). Co-administration of canagliflozin (300 mg once daily) and metformin (2,000 mg once daily) had no clinically relevant effect on the pharmacokinetics of either canagliflozin or metformin.

Canagliflozin

Pharmacodynamic interactions

Diuretics

Canagliflozin may add to the effect of diuretics and may increase the risk of dehydration and hypotension (see section 4.4).

Canagliflozin is not recommended for use in patients receiving loop diuretics.

Insulin and insulin secretagogues

Insulin and insulin secretagogues, such as sulphonylureas, can cause hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with Vokanamet (see sections 4.2 and 4.8).

Pharmacokinetic interactions

Effects of other medicinal products on canagliflozin

The metabolism of canagliflozin is primarily via glucuronide conjugation mediated by UDP glucuronosyl transferase 1A9 (UGT1A9) and 2B4 (UGT2B4). Canagliflozin is transported by P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP).

Enzyme inducers (such as St. John's wort [*Hypericum perforatum*], rifampicin, barbiturates, phenytoin, carbamazepine, ritonavir, efavirenz) may give rise to decreased exposure of canagliflozin. Following co-administration of canagliflozin with rifampicin (an inducer of various active transporters and medicinal product-metabolising enzymes), 51% and 28% decreases in canagliflozin systemic exposure (area under the curve, AUC) and peak concentration (C_{max}) were observed. These decreases in exposure to canagliflozin may decrease efficacy.

If a combined inducer of these UGT enzymes and transport proteins must be co-administered with canagliflozin, monitoring of glycaemic control to assess response to canagliflozin is appropriate. If an inducer of these UGT enzymes must be co-administered with canagliflozin, increasing the dose to Vokanamet containing 150 mg twice daily may be considered if patients are currently tolerating canagliflozin 50 mg twice daily and require additional glycaemic control (see sections 4.2 and 4.4).

Cholestyramine may potentially reduce canagliflozin exposure. Dosing of canagliflozin should occur at least 1 hour before or 4-6 hours after administration of a bile acid sequestrant to minimise possible interference with their absorption.

Interaction studies suggest that the pharmacokinetics of canagliflozin are not altered by metformin, hydrochlorothiazide, oral contraceptives (ethinyl estradiol and levonorgestrol), ciclosporin, and/or probenecid.

Effects of canagliflozin on other medicinal products

Digoxin
The combination of canagliflozin 300 mg once daily for 7 days with a single dose of digoxin 0.5 mg followed by 0.25 mg daily for 6 days resulted in a 20% increase in AUC and a 36% increase in C_{max} of digoxin, probably due to inhibition of P-gp. Canagliflozin has been observed to inhibit P-gp *in vitro*. Patients taking digoxin or other cardiac glycosides (e.g., digitoxin) should be monitored appropriately.

Lithium
The concomitant use of an SGLT2 inhibitor with lithium may decrease serum lithium concentrations. Monitor serum lithium concentration more closely during treatment with canagliflozin, especially during initiation and dosage changes.

Dabigatran
The effect of concomitant administration of canagliflozin (a weak P-gp inhibitor) on dabigatran etexilate (a P-gp substrate) has not been studied. As dabigatran concentrations may be increased in the presence of canagliflozin, monitoring (looking for signs of bleeding or anaemia) should be exercised when dabigatran is combined with canagliflozin.

Simvastatin
The combination of canagliflozin 300 mg once daily for 6 days with a single dose of simvastatin (CYP3A4 substrate) 40 mg resulted in a 12% increase in AUC and a 9% increase in C_{max} of simvastatin and an 18% increase in AUC and a 26% increase in C_{max} of simvastatin acid. The increases in simvastatin and simvastatin acid exposures are not considered clinically relevant.

Inhibition of BCRP by canagliflozin cannot be excluded at an intestinal level and increased exposure may therefore occur for medicinal products transported by BCRP, e.g., certain statins like rosuvastatin and some anti-cancer medicinal products.

In interaction studies, canagliflozin at steady-state had no clinically relevant effect on the pharmacokinetics of metformin, oral contraceptives (ethinyl estradiol and levonorgestrol), glibenclamide, paracetamol, hydrochlorothiazide, or warfarin.

Medicinal product/laboratory test interference

1,5-AG assay

Increases in urinary glucose excretion with canagliflozin can falsely lower 1,5-anhydroglucitol (1,5-AG) levels and make measurements of 1,5-AG unreliable in assessing glycaemic control. Therefore, 1,5-AG assays should not be used for assessment of glycaemic control in patients on Vokanamet. For further detail, it may be advisable to contact the specific manufacturer of the 1,5-AG assay.

Metformin

Concomitant use not recommended

Alcohol

Alcohol intoxication is associated with an increased risk of lactic acidosis (particularly in cases of fasting, malnutrition, or hepatic impairment) due to the metformin active substance of Vokanamet (see section 4.4). Consumption of alcohol and medicinal products containing alcohol should be avoided.

Iodinated contrast agents

The intravascular administration of iodinated contrast agents in radiological studies may lead to renal failure, resulting in metformin accumulation and a risk of lactic acidosis. Therefore, Vokanamet must be discontinued prior to, or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable (see sections 4.2 and 4.4).

Cationic medicinal products

Cationic medicinal products that are eliminated by renal tubular secretion (e.g., cimetidine) may interact with metformin by competing for common renal tubular transport systems. A study conducted in seven normal healthy volunteers showed that cimetidine, administered as 400 mg twice daily, increased metformin AUC by 50% and C_{max} by 81%. Therefore, close monitoring of glycaemic control, dose adjustment within the recommended posology and changes in diabetic treatment should be considered when cationic medicinal products that are eliminated by renal tubular secretion are co-administered (see sections 4.4 and 5.1).

Combinations requiring precautions for use

Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with Vokanamet, close monitoring of renal function is necessary.

Glucocorticoids (given by systemic and local routes), beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be informed and more frequent blood glucose monitoring performed, especially at the beginning of treatment with such medicinal products. If necessary, the dose of glucose-lowering medicinal products should be adjusted during therapy with the other medicinal product and on its discontinuation.

Due to their potential to decrease renal function, diuretics (especially loop diuretics) may increase the risk of lactic acidosis associated with metformin.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of canagliflozin alone or Vokanamet in pregnant women. Studies in animals with canagliflozin have shown reproductive toxicity (see section 5.3).

A large amount of data from the use of metformin in pregnant women (more than 1,000 exposed outcomes) from a register-based cohort study and published data (meta-analyses, clinical studies, and registries) do not indicate an increased risk of congenital malformations. Animal studies with metformin do not indicate harmful effects with respect to pregnancy, embryonic or foetal development, parturition, or postnatal development (see section 5.3).

Vokanamet should not be used during pregnancy. When pregnancy is detected, treatment with Vokanamet should be discontinued.

Breast-feeding

No studies in lactating animals have been conducted with the combined active substances of Vokanamet. It is unknown whether canagliflozin and/or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of canagliflozin/metabolites in milk, as well as pharmacologically mediated effects in breast-feeding offspring and juvenile rats exposed to canagliflozin (see section 5.3). Metformin is excreted into human breast milk in small amounts. A risk to newborns/infants cannot be excluded. Vokanamet should not be used during breast-feeding.

Fertility

The effect of Vokanamet on fertility in humans has not been studied. No effects of canagliflozin or metformin on fertility were observed in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Vokanamet has no or negligible influence on the ability to drive and use machines. However, patients should be alerted to the risk of hypoglycaemia when Vokanamet is used as add-on therapy with insulin or an insulin secretagogue, and to the elevated risk of adverse reactions related to volume depletion, such as postural dizziness (see sections 4.2, 4.4, and 4.8).

4.8 Undesirable effects

Canagliflozin

Summary of the safety profile

The safety of canagliflozin was evaluated in 22,645 patients with type 2 diabetes, including the evaluation of canagliflozin in combination with metformin in 16,334 patients. In addition, an 18-week double-blind, placebo-controlled phase 2 study with twice daily dosing (canagliflozin 50 mg or 150 mg as add-on therapy with metformin 500 mg) was conducted in 279 patients in which 186 patients were treated with canagliflozin as add-on therapy with metformin.

The primary assessment of safety and tolerability was conducted in a pooled analysis (N = 2,313) of four 26-week placebo-controlled clinical studies (monotherapy and add-on therapy with metformin, metformin and a sulphonylurea, and metformin and pioglitazone). The most commonly reported adverse reactions during treatment were hypoglycaemia in combination with insulin or a

sulphonylurea, vulvovaginal candidiasis, urinary tract infection, and polyuria or pollakiuria (i.e., urinary frequency). Adverse reactions leading to discontinuation of ≥ 0.5% of all canagliflozin-treated patients in these studies were vulvovaginal candidiasis (0.7% of female patients) and balanitis or balanoposthitis (0.5% of male patients). Additional safety analyses (including long-term data) from data across the entire canagliflozin programme (placebo- and active-controlled studies) were conducted to assess reported adverse events in order to identify adverse reactions (see table 2) (see sections 4.2 and 4.4).

Tabulated list of adverse reactions

Adverse reactions in table 2 are based on the pooled analysis of the placebo- and active-controlled studies described above. Adverse reactions reported from world-wide postmarketing use of canagliflozin are also included in this tabulation. Adverse reactions listed below are classified according to frequency and system organ class. Frequency categories are defined according to the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Table 2: Tabulated list of adverse reactions (MedDRA) from placebo-[e] and active-controlled studies[e] and from postmarketing experience

System organ class Frequency	**Adverse reaction**
Infections and infestations	
very common	Vulvovaginal candidiasis[b, j]
common	Balanitis or balanoposthitis[b, k], Urinary tract infection[c] (pyelonephritis and urosepsis have been reported postmarketing)
not known	Necrotising fasciitis of the perineum (Fournier's gangrene)[d]
Immune system disorders	
rare	Anaphylactic reaction
Metabolism and nutrition disorders	
very common	Hypoglycaemia in combination with insulin or sulphonylurea[c]
uncommon	Dehydration[a]
rare	Diabetic ketoacidosis[b]
Nervous system disorders	
uncommon	Dizziness postural[a], Syncope[a]
Vascular disorders	
uncommon	Hypotension[a], Orthostatic hypotension[a]
Gastrointestinal disorders	
common	Constipation, Thirst[f], Nausea
Skin and subcutaneous tissue disorders	
uncommon	Photosensitivity, Rash[g], Urticaria
rare	Angioedema
Musculoskeletal and connective tissue disorders	
uncommon	Bone fracture[h]
Renal and urinary disorders	
common	Polyuria or Pollakiuria[i]

uncommon	Renal failure (mainly in the context of volume depletion)
Investigations	
common	Dyslipidaemia[l], Haematocrit increased[b, m]
uncommon	Blood creatinine increased[b, n], Blood urea increased[b, o], Blood potassium increased[b, p], Blood phosphate increased[q]
Surgical and medical procedures	
uncommon	Lower limb amputations (mainly of the toe and midfoot) especially in patients at high risk for heart disease[b]

[a] Related to volume depletion; see section 4.4 and description of adverse reaction (AR) below.

[b] See section 4.4 and description of AR below.

[c] See description of AR below.

[d] See section 4.4.

[e] Safety data profiles from individual pivotal studies (including studies in moderately renally impaired patients; older patients [≥ 55 years of age to ≤ 80 years of age]; patients with increased CV- and renal-risk) were generally consistent with the adverse reactions identified in this table.

[f] Thirst includes the terms thirst, dry mouth, and polydipsia.

[g] Rash includes the terms rash erythematous, rash generalised, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, and rash vesicular.

[h] Related to bone fracture; see description of AR below.

[i] Polyuria or pollakiuria includes the terms polyuria, pollakiuria, micturition urgency, nocturia, and urine output increased.

[j] Vulvovaginal candidiasis includes the terms vulvovaginal candidiasis, vulvovaginal mycotic infection, vulvovaginitis, vaginal infection, vulvitis, and genital infection fungal.

[k] Balanitis or balanoposthitis includes the terms balanitis, balanoposthitis, balanitis candida, and genital infection fungal.

[l] Mean percent increases from baseline for canagliflozin 100 mg and 300 mg *versus* placebo, respectively, were total cholesterol 3.4% and 5.2% *versus* 0.9%; HDL-cholesterol 9.4% and 10.3% *versus* 4.0%; LDL-cholesterol 5.7% and 9.3% *versus* 1.3%; non-HDL-cholesterol 2.2% and 4.4% *versus* 0.7%; triglycerides 2.4% and 0.0% *versus* 7.6%.

[m] Mean changes from baseline in haematocrit were 2.4% and 2.5% for canagliflozin 100 mg and 300 mg, respectively, compared to 0.0% for placebo.

[n] Mean percent changes from baseline in creatinine were 2.8% and 4.0% for canagliflozin 100 mg and 300 mg, respectively, compared to 1.5% for placebo.

[o] Mean percent changes from baseline in blood urea nitrogen were 17.1% and 18.0% for canagliflozin 100 mg and 300 mg, respectively, compared to 2.7% for placebo.

[p] Mean percent changes from baseline in blood potassium were 0.5% and 1.0% for canagliflozin 100 mg and 300 mg, respectively, compared to 0.6% for placebo.

[q] Mean percent changes from baseline in serum phosphate were 3.6% and 5.1% for canagliflozin 100 mg and 300 mg, compared to 1.5% for placebo.

Description of selected adverse reactions

Lower limb amputation

In patients with type 2 diabetes who had established cardiovascular disease or at least two risk factors for cardiovascular disease, canagliflozin was associated with an increased risk of lower limb amputation as observed in the Integrated CANVAS Program comprised of CANVAS and CANVAS-R, two large, long-term, randomised, placebo-controlled trials evaluating 10,134 patients. The imbalance occurred as early as the first 26 weeks of therapy. Patients in CANVAS and CANVAS-R were followed for an average of 5.7 and 2.1 years, respectively. Regardless of treatment with canagliflozin or placebo, the risk of amputation was highest in patients with a baseline history of prior amputation, peripheral vascular disease, and neuropathy. The risk of lower limb amputation was not dose-dependent. The amputation results for the Integrated CANVAS Program are shown in table 3.

There was no difference in risk of lower limb amputations associated with the use of canagliflozin 100 mg relative to placebo (1.2 vs 1.1 events per 100 patient-years, respectively [HR: 1.11; 95% CI 0.79, 1.56]) in a long-term renal outcomes study of 4,397 patients with type 2 diabetes and diabetic kidney disease (see section 4.4). In other type 2 diabetes studies with canagliflozin, which enrolled a general diabetic population of 8,114 patients, no difference in lower limb amputation risk was observed relative to control.

Table 3: Integrated analysis of amputations in CANVAS and CANVAS-R

	Placebo N = 4,344	**canagliflozin N = 5,790**
Total number of subjects with events, n (%)	47 (1.1)	140 (2.4)
Incidence rate (per 100 patient-years)	0.34	0.63
HR (95% CI) vs. placebo		1.97 (1.41, 2.75)
Minor amputation, n (%)*	34/47 (72.3)	99/140 (70.7)
Major amputation, n (%)†	13/47 (27.7)	41/140 (29.3)

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. The percentage of minor and major amputations is based on the highest level amputation for each patient.

* Toe and midfoot

† Ankle, below knee and above knee

Of the subjects, within the CANVAS Program, who had an amputation, the toe and midfoot were the most frequent sites (71%) in both treatment groups (see table 3). Multiple amputations (some involving both lower limbs) were observed infrequently and in similar proportions in both treatment groups.

Lower limb infections, diabetic foot ulcers, peripheral arterial disease, and gangrene, were the most common medical events associated with the need for an amputation in both treatment groups (see section 4.4).

Adverse reactions related to volume depletion

In the pooled analysis of the four 26-week, placebo-controlled studies, the incidence of all adverse reactions related to volume depletion (e.g., postural dizziness, orthostatic hypotension, hypotension, dehydration, and syncope) was 1.2% for canagliflozin 100 mg once daily, 1.3% for canagliflozin 300 mg once daily, and 1.1% for placebo. The incidence with canagliflozin treatment in the two active-controlled studies was similar to comparators.

In one of the dedicated long-term cardiovascular studies (CANVAS), where patients were generally older with a higher rate of diabetes complications, the incidence rates of adverse reactions related to volume depletion were 2.3 with canagliflozin 100 mg, 2.9 with canagliflozin 300 mg, and 1.9 with placebo, events per 100 patient-years.

To assess risk factors for these adverse reactions, a larger pooled analysis (N = 12,441) of patients from 13 controlled phase 3 and phase 4 studies including both doses of canagliflozin was conducted. In this pooled analysis, patients on loop diuretics, patients with a baseline eGFR 30 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2, and patients ≥ 75 years of age had generally higher incidences of these adverse reactions. For patients on loop diuretics, the incidence rates were 5.0 on canagliflozin 100 mg and 5.7 on canagliflozin 300 mg compared to 4.1 events per 100 patient-years of exposure in the control group. For patients with a baseline eGFR 30 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2, the incidence rates were 5.2 on canagliflozin 100 mg and 5.4 on canagliflozin 300 mg compared to 3.1 events per 100 patient-years of exposure in the control group. In patients ≥ 75 years of age, the incidence rates were 5.3 on canagliflozin 100 mg and 6.1 on canagliflozin 300 mg compared to 2.4 events per 100 patient-years of exposure in the control group (see sections 4.2 and 4.4).

In the dedicated cardiovascular study and the larger pooled analysis, as well as in a dedicated renal outcomes study, discontinuations due to adverse reactions related to volume depletion and serious adverse reactions related to volume depletion were not increased with canagliflozin.

Hypoglycaemia in add-on therapy with insulin or insulin secretagogues

The frequency of hypoglycaemia was low (approximately 4%) among treatment groups, including placebo, when used as monotherapy or as an add-on to metformin. When canagliflozin was added to insulin therapy, hypoglycaemia was observed in 49.3%, 48.2%, and 36.8% of patients treated with canagliflozin 100 mg once daily, canagliflozin 300 mg once daily, and placebo, respectively, and severe hypoglycaemia occurred in 1.8%, 2.7%, and 2.5% of patients treated with canagliflozin 100 mg once daily, canagliflozin 300 mg once daily, and placebo, respectively. When canagliflozin was added to a sulphonylurea therapy, hypoglycaemia was observed in 4.1%, 12.5%, and 5.8% of patients treated with canagliflozin 100 mg once daily, canagliflozin 300 mg once daily, and placebo, respectively (see sections 4.2 and 4.5).

Genital mycotic infections

Vulvovaginal candidiasis (including vulvovaginitis and vulvovaginal mycotic infection) was reported in 10.4% and 11.4% of female patients treated with canagliflozin 100 mg once daily and canagliflozin 300 mg once daily, respectively, compared to 3.2% in placebo-treated female patients. Most reports of vulvovaginal candidiasis occurred during the first four months of treatment with canagliflozin. Among female patients taking canagliflozin, 2.3% experienced more than one infection. Overall, 0.7% of all female patients discontinued canagliflozin due to vulvovaginal candidiasis (see section 4.4). In the CANVAS Program, median duration of the infection was longer in the canagliflozin group compared to the placebo group.

Candidal balanitis or balanoposthitis occurred in male patients at a rate of 2.98 and 0.79 events per 100 patient-years on canagliflozin and placebo, respectively. Among male patients taking canagliflozin, 2.4% had more than one infection. Discontinuation of canagliflozin by male patients due to candidal balanitis or balanoposthitis occurred at a rate of 0.37 events per 100 patient-years. Phimosis was reported at a rate of 0.39 and 0.07 events per 100 patient-years on canagliflozin and placebo, respectively. Circumcision was performed at rates of 0.31 and 0.09 events per 100 patient-years on canagliflozin and placebo, respectively (see section 4.4).

Urinary tract infections

In clinical studies, urinary tract infections were more frequently reported for canagliflozin 100 mg and 300 mg once daily (5.9% *versus* 4.3%, respectively) compared to 4.0% with placebo. Most infections were mild to moderate with no increase in the occurrence of serious adverse reactions. In these studies, subjects responded to standard treatments while continuing canagliflozin treatment.

However, post-marketing cases of complicated urinary tract infections including pyelonephritis and urosepsis have been reported in patients treated with canagliflozin, frequently leading to treatment interruption.

Bone fracture

In a cardiovascular study (CANVAS) of 4,327 treated subjects with established or at least two risk factors for cardiovascular disease, the incidence rates of all adjudicated bone fracture were 1.6, 1.8, and 1.1 per 100 patient-years of follow-up to canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively, with the fracture imbalance initially occurring within the first 26 weeks of therapy.

In two other long-term studies and in studies conducted in the general diabetes population, no difference in fracture risk was observed with canagliflozin relative to control. In a second cardiovascular study (CANVAS-R) of 5,807 treated subjects with established or at least two risk

factors for cardiovascular disease, the incidence rates of all adjudicated bone fracture were 1.1 and 1.3 events per 100 patient-years of follow-up to canagliflozin and placebo, respectively.

In a long-term renal outcomes study of 4,397 treated subjects with type 2 diabetes and diabetic kidney disease, the incidence rates of all adjudicated bone fracture were 1.2 events per 100 patient-years of follow-up for both canagliflozin 100 mg and placebo. In other type 2 diabetes studies with canagliflozin, which enrolled a general diabetes population of 7,729 patients and where bone fractures were adjudicated, the incidence rates of all adjudicated bone fracture were 1.2 and 1.1 per 100 patient-years of follow-up to canagliflozin and control, respectively. After 104 weeks of treatment, canagliflozin did not adversely affect bone mineral density.

Special populations

Elderly
In a pooled analysis of 13 placebo-controlled and active-controlled studies, the safety profile of canagliflozin in elderly patients was generally consistent with younger patients. Patients ≥ 75 years of age had a higher incidence of adverse reactions related to volume depletion (such as postural dizziness, orthostatic hypotension, hypotension) with incidence rates of 5.3, 6.1 and 2.4 events per 100 patient-years of exposure for canagliflozin 100 mg once daily, canagliflozin 300 mg once daily, and in the control group, respectively. Decreases in eGFR (-3.4 and -4.7 mL/min/1.73 m^2) were reported with canagliflozin 100 mg and canagliflozin 300 mg, respectively, compared to the control group (-4.2 mL/min/1.73 m^2). Mean baseline eGFR was 62.5, 64.7, and 63.5 mL/min/1.73 m^2 for canagliflozin 100 mg, canagliflozin 300 mg, and the control group, respectively (see sections 4.2 and 4.4).

Renal impairment
Patients with a baseline eGFR < 60 mL/min/1.73 m^2 had a higher incidence of adverse reactions associated with volume depletion (e.g., postural dizziness, orthostatic hypotension, hypotension) with incidence rates of 5.3, 5.1, and 3.1 events per 100 patient-years of exposure for canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively (see sections 4.2 and 4.4).

The overall incidence rate of elevated serum potassium was higher in patients with moderate renal impairment with incidence rates of 4.9, 6.1, and 5.4 events per 100 patient-years of exposure for canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively. In general, elevations were transient and did not require specific treatment.

In patients with moderate renal impairment, increases in serum creatinine of 9.2 μmol/L and BUN of approximately 1.0 mmol/L were observed with both doses of canagliflozin.

The incidence rates for larger decreases in eGFR (> 30%) at any time during treatment were 7.3, 8.1, and 6.5 events per 100 patient-years of exposure for canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively. At the last post-baseline value, incidence rates of such decreases were 3.3 for patients treated with canagliflozin 100 mg, 2.7 for canagliflozin 300 mg, and 3.7 events per 100 patient-years of exposure for placebo (see section 4.4).

Patients treated with canagliflozin regardless of baseline eGFR experienced an initial fall in mean eGFR. Thereafter, eGFR was maintained or gradually increased during continued treatment. Mean eGFR returned to baseline after treatment discontinuation suggesting that haemodynamic changes may play a role in these renal function changes.

Metformin

Table 4 presents adverse reactions by SOC and by frequency category reported in patients who received metformin as monotherapy and that were not observed in patients receiving canagliflozin. Frequency categories are based on information available from the metformin Summary of Product Characteristics.

Table 4: The frequency of metformin adverse reactions identified from clinical study and postmarketing data

System organ class Frequency	**Adverse reaction**
Metabolism and nutrition disorders	
common	Vitamin B_{12} decrease/deficiency[a]
very rare	Lactic acidosis
Nervous system disorders	
common	Taste disturbance
Gastrointestinal disorders	
very common	Gastro-intestinal symptoms[b]
Skin and subcutaneous tissue disorders	
very rare	Erythema, Pruritus, Urticaria
Hepatobiliary disorders	
very rare	Liver function test abnormal, Hepatitis

[a] Metformin may commonly reduce vitamin B_{12} serum levels, which may result in clinically significant vitamin B_{12} deficiency (e.g., megaloblastic anaemia). The risk of low vitamin B_{12} levels increases with increasing metformin dose, treatment duration, and/or in patients with risk factors known to cause vitamin B_{12} deficiency. Periodic monitoring of vitamin B_{12} levels is recommended in these patients.

[b] Gastrointestinal symptoms such as nausea, vomiting, diarrhoea, abdominal pain and loss of appetite occur most frequently during initiation of therapy and resolve spontaneously in most cases.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Canagliflozin

Single doses up to 1,600 mg of canagliflozin in healthy subjects and canagliflozin 300 mg twice daily for 12 weeks in patients with type 2 diabetes were generally well-tolerated.

Metformin

Hypoglycaemia has not been seen with metformin hydrochloride doses of up to 85 g; although, lactic acidosis has occurred in such circumstances. High overdose of metformin or concomitant risks may lead to lactic acidosis. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and metformin is haemodialysis.

Therapy

In the event of an overdose of Vokanamet, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute clinical measures as dictated by the patient's clinical status. The most effective method to remove lactate and metformin is haemodialysis. Canagliflozin was negligibly removed during a 4-hour haemodialysis session. Canagliflozin is not expected to be dialysable by peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, combinations of blood glucose lowering drugs, ATC code: A10BD16.

Mechanism of action

Vokanamet combines two oral glucose-lowering medicinal products with different and complementary mechanisms of action to improve glycaemic control in patients with type 2 diabetes: canagliflozin, an inhibitor of SGLT2 transporter, and metformin hydrochloride, a member of the biguanide class.

Canagliflozin

The SGLT2 transporter, expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Patients with diabetes have been shown to have elevated renal glucose reabsorption which may contribute to persistent elevated blood glucose concentrations. Canagliflozin is an orally-active inhibitor of SGLT2. By inhibiting SGLT2, canagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose (RT_G), and thereby increases UGE, lowering elevated plasma glucose concentrations by this insulin-independent mechanism in patients with type 2 diabetes. The increased UGE with SGLT2 inhibition also translates to an osmotic diuresis, with the diuretic effect leading to a reduction in systolic blood pressure; the increase in UGE results in a loss of calories and therefore a reduction in body weight, as has been demonstrated in studies of patients with type 2 diabetes.

Canagliflozin's action to increase UGE directly lowering plasma glucose is independent of insulin. Improvement in homeostasis model assessment for beta-cell function (HOMA beta-cell) and improved beta-cell insulin secretion response to a mixed-meal challenge has been observed in clinical studies with canagliflozin.

In phase 3 studies, pre-meal administration of canagliflozin 300 mg once daily provided a greater reduction in postprandial glucose excursion than observed with the 100 mg once daily dose. This effect at the 300 mg dose of canagliflozin may, in part, be due to local inhibition of intestinal SGLT1 (an important intestinal glucose transporter) related to transient high concentrations of canagliflozin in the intestinal lumen prior to medicinal product absorption (canagliflozin is a low potency inhibitor of the SGLT1 transporter). Studies have shown no glucose malabsorption with canagliflozin.

Metformin

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via three mechanisms:
- by reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
- in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
- and delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of the membrane glucose transporters GLUT-1 and GLUT-4.

In humans, independently of its action on glycaemia, metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term, or long-term clinical studies: metformin reduces total cholesterol, LDL-C, and triglyceride levels.

Pharmacodynamic effects of canagliflozin

Following single and multiple oral doses of canagliflozin to patients with type 2 diabetes, dose-dependent decreases in RT_G and increases in UGE were observed. From a starting value of RT_G of approximately 13 mmol/L, maximal suppression of 24-hour mean RT_G was seen with the 300 mg daily dose to approximately 4 mmol/L to 5 mmol/L in patients with type 2 diabetes in phase 1 studies, suggesting a low risk for treatment-induced hypoglycaemia. The reductions in RT_G led to increased UGE in subjects with type 2 diabetes treated with either 100 mg or 300 mg once daily of canagliflozin ranging from 77 g/day to 119 g/day across the phase 1 studies; the UGE observed translates to a loss of 308 kcal/day to 476 kcal/day. The reductions in RT_G and increases in UGE were sustained over a 26-week dosing period in patients with type 2 diabetes. Moderate increases (generally < 400 mL to 500 mL) in daily urine volume were seen that attenuated over several days of dosing. Urinary uric acid excretion was transiently increased by canagliflozin (increased by 19% compared to baseline on day 1 and then attenuating to 6% on day 2 and 1% on day 13). This was accompanied by a sustained reduction in serum uric acid concentration of approximately 20%.

In a single-dose study in patients with type 2 diabetes, treatment with 300 mg before a mixed meal delayed intestinal glucose absorption and reduced postprandial glucose through both a renal and a non-renal mechanism.

Clinical efficacy and safety

Both improvement in glycaemic control and reduction of cardiovascular morbidity and mortality are an integral part of the treatment of type 2 diabetes.

The co-administration of canagliflozin and metformin has been studied in patients with type 2 diabetes inadequately controlled on metformin either alone or in combination with other glucose-lowering medicinal products.

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.

Canagliflozin

Glycaemic efficacy and safety

A total of 10,501 patients with type 2 diabetes participated in ten double-blind, controlled clinical efficacy and safety studies conducted to evaluate the effects of canagliflozin on glycaemic control, including 5,151 patients treated with canagliflozin in combination with metformin. The racial distribution of patients who received canagliflozin was 72% White, 16% Asian, 5% Black, and 8% other groups. 17% of patients were Hispanic. 58% of patients were male. Patients had an overall mean age of 59.5 years (range 21 years to 96 years), with 3,135 patients ≥ 65 years of age and 513 patients ≥ 75 years of age. 58% of patients had a body mass index (BMI) ≥ 30 kg/m^2. In the clinical development programme, 1,085 patients with a baseline eGFR 30 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2 were evaluated.

Placebo-controlled studies

Canagliflozin was studied as dual therapy with metformin, dual therapy with a sulphonylurea, triple therapy with metformin and a sulphonylurea, triple therapy with metformin and pioglitazone, as an add-on therapy with insulin, and as monotherapy (table 5). In general, canagliflozin produced clinically and statistically significant ($p < 0.001$) results relative to placebo in glycaemic control, including glycosylated haemoglobin (HbA_{1c}), the percentage of patients achieving $HbA_{1c} < 7\%$, change from baseline fasting plasma glucose (FPG), and 2-hour postprandial glucose (PPG). In addition, reductions in body weight and systolic blood pressure relative to placebo were observed.

Furthermore, canagliflozin was studied as triple therapy with metformin and sitagliptin and dosed with a titration regimen, using a starting dose of 100 mg and titrated to 300 mg as early as week 6 in patients requiring additional glycaemic control who had appropriate eGFR and were tolerating canagliflozin 100 mg (table 5). Canagliflozin dosed with a titration regimen produced clinically and statistically significant ($p < 0.001$) results relative to placebo in glycaemic control, including HbA_{1c} and change from baseline FPG, and a statistically significant ($p < 0.01$) improvement in the percentage of patients achieving $HbA_{1c} < 7\%$. In addition, reductions in body weight and systolic blood pressure relative to placebo were observed.

Table 5: Efficacy results from placebo-controlled clinical studies[a]

Dual therapy with metformin (26 weeks)			
	Canagliflozin + metformin		**Placebo + metformin (N = 183)**
	100 mg (N = 368)	**300 mg (N = 367)**	
HbA_{1c} (%)			
Baseline (mean)	7.94	7.95	7.96
Change from baseline (adjusted mean)	-0.79	-0.94	-0.17
Difference from placebo (adjusted mean) (95% CI)	-0.62[b] (-0.76; -0.48)	-0.77[b] (-0.91; -0.64)	N/A[c]
Patients (%) achieving $HbA_{1c} < 7\%$	45.5[b]	57.8[b]	29.8
Body weight			
Baseline (mean) in kg	88.7	85.4	86.7
% change from baseline (adjusted mean)	-3.7	-4.2	-1.2
Difference from placebo (adjusted mean) (95% CI)	-2.5[b] (-3.1; -1.9)	-2.9[b] (-3.5; -2.3)	N/A[c]
Triple therapy with metformin and sulphonylurea (26 weeks)			
	Canagliflozin + metformin and sulphonylurea		**Placebo + metformin and sulphonylurea (N = 156)**
	100 mg (N = 157)	**300 mg (N = 156)**	
HbA_{1c} (%)			
Baseline (mean)	8.13	8.13	8.12
Change from baseline (adjusted mean)	-0.85	-1.06	-0.13
Difference from placebo (adjusted mean) (95% CI)	-0.71[b] (-0.90; -0.52)	-0.92[b] (-1.11; -0.73)	N/A[c]
Patients (%) achieving $HbA_{1c} < 7\%$	43.2[b]	56.6[b]	18.0
Body weight			
Baseline (mean) in kg	93.5	93.5	90.8
% change from baseline (adjusted mean)	-2.1	-2.6	-0.7
Difference from placebo (adjusted mean) (95% CI)	-1.4[b] (-2.1; -0.7)	-2.0[b] (-2.7; -1.3)	N/A[c]
Add-on therapy with insulin[d] (18 weeks)			
	Canagliflozin + insulin		**Placebo + insulin (N = 565)**
	100 mg (N = 566)	**300 mg (N = 587)**	
HbA_{1c} (%)			
Baseline (mean)	8.33	8.27	8.20
Change from baseline (adjusted mean)	-0.63	-0.72	0.01
Difference from placebo (adjusted mean) (95% CI)	-0.65[b] (-0.73; -0.56)	-0.73[b] (-0.82; -0.65)	N/A[c]
Patients (%) achieving $HbA_{1c} < 7\%$	19.8[b]	24.7[b]	7.7
Body weight			
Baseline (mean) in kg	96.9	96.7	97.7

% change from baseline (adjusted mean)	-1.8	-2.3	0.1
Difference from placebo (adjusted mean) (97.5% CI)	-1.9[b] (-2.2; -1.5)	-2.4[b] (-2.8; -2.0)	N/A[c]
Triple therapy with metformin and sitagliptin[e] (26 weeks)			
	Canagliflozin + metformin and sitagliptin[g] (N = 107)	**Placebo + metformin and sitagliptin (N = 106)**	
HbA_{1c} (%)			
Baseline (mean)	8.53	8.38	
Change from baseline (adjusted mean)	-0.91	-0.01	
Difference from placebo (adjusted mean) (95% CI)	-0.89[b] (-1.19; -0.59)		
Patients (%) achieving HbA_{1c} < 7%	32[f]	12	
Fasting plasma glucose (mg/dL)			
Baseline (mean)	186	180	
Change from baseline (adjusted mean)	-30	-3	
Difference from placebo (adjusted mean) (95% CI)	-27[b] (-40; -14)		
Body weight			
Baseline (mean) in kg	93.8	89.9	
% change from baseline (adjusted mean)	-3.4	-1.6	
Difference from placebo (adjusted mean) (95% CI)	-1.8[b] (-2.7; -0.9)		

[a] Intent-to-treat population using last observation in study prior to glycaemic rescue therapy.

[b] $p < 0.001$ compared to placebo.

[c] Not applicable.

[d] Canagliflozin as add-on therapy to insulin (with or without other glucose-lowering medicinal products).

[e] Canagliflozin 100 mg uptitrated to 300 mg

[f] $p < 0.01$ compared to placebo

[g] 90.7% of subjects in the canagliflozin group uptitrated to 300 mg

In addition to the studies presented above, glycaemic efficacy results observed in an 18-week dual therapy sub-study with a sulphonylurea and a 26-week triple therapy study with metformin and pioglitazone were generally comparable with those observed in other studies.

A dedicated study demonstrated that co-administration of canagliflozin 50 mg and 150 mg dosed twice daily as dual therapy with metformin produced clinically and statistically significant results relative to placebo in glycaemic control, including HbA_{1c}, the percentage of patients achieving HbA_{1c} < 7%, change from baseline FPG, and in reductions in body weight as shown in table 6.

Table 6: Efficacy results from placebo-controlled clinical study of canagliflozin dosed twice daily[a]

	Canagliflozin		**Placebo (N = 93)**
	50 mg twice daily (N = 93)	**150 mg twice daily (N = 93)**	
HbA_{1c} (%)			
Baseline (mean)	7.63	7.53	7.66
Change from baseline (adjusted mean)	-0.45	-0.61	-0.01
Difference from placebo (adjusted mean) (95% CI)	-0.44[b] (-0.637; -0.251)	-0.60[b] (-0.792; -0.407)	N/A[c]
Patients (%) achieving HbA_{1c} < 7%	47.8[d]	57.1[b]	31.5

Body weight			
Baseline (mean) in kg	90.59	90.44	90.37
% change from baseline (adjusted mean)	-2.8	-3.2	-0.6
Difference from placebo (adjusted mean) (95% CI)	-2.2[b] (-3.1; -1.3)	-2.6[b] (-3.5; -1.7)	N/A[c]

[a] Intent-to-treat population using last observation in study.

[b] $p < 0.001$ compared to placebo.

[c] Not applicable.

[d] $p = 0.013$ compared to placebo.

Active-controlled studies

Canagliflozin was compared to glimepiride as dual therapy with metformin and compared to sitagliptin as triple therapy with metformin and a sulphonylurea (table 7). Canagliflozin 100 mg once daily as dual therapy with metformin produced similar reductions in HbA_{1c} from baseline and 300 mg produced superior ($p < 0.05$) reductions in HbA_{1c} compared to glimepiride, thus demonstrating non-inferiority. A lower proportion of patients treated with canagliflozin 100 mg once daily (5.6%) and canagliflozin 300 mg once daily (4.9%) experienced at least one episode/event of hypoglycaemia over 52 weeks of treatment compared to the group treated with glimepiride (34.2%). In a study comparing canagliflozin 300 mg once daily to sitagliptin 100 mg in triple therapy with metformin and a sulphonylurea, canagliflozin demonstrated non-inferior ($p < 0.05$) and superior ($p < 0.05$) reduction in HbA_{1c} relative to sitagliptin. The incidence of hypoglycaemia episodes/events with canagliflozin 300 mg once daily and sitagliptin 100 mg was 40.7% and 43.2%, respectively. Significant improvements in body weight and reductions in systolic blood pressure compared to both glimepiride and sitagliptin were also observed.

Table 7: Efficacy results from active-controlled clinical studies[a]

Compared to glimepiride as dual therapy with metformin (52 weeks)			
	Canagliflozin + metformin		**Glimepiride (titrated) + metformin (N = 482)**
	100 mg (N = 483)	**300 mg (N = 485)**	
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[b] (−0.11; 0.09)	-0.12[b] (−0.22; −0.02)	N/A[c]
Patients (%) achieving $HbA_{1c} < 7\%$	53.6	60.1	55.8
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[b] (−5.7; −4.7)	-5.7[b] (−6.2; −5.1)	N/A[c]
Compared to sitagliptin as triple therapy with metformin and sulphonylurea (52 weeks)			
	Canagliflozin 300 mg + metformin and sulphonylurea (N = 377)		**Sitagliptin 100 mg + metformin and sulphonylurea (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[b] (-0.50; -0.25)		N/A

Patients (%) achieving HbA_{1c} < 7%	47.6	35.3
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[d] (-3.3; -2.2)	N/A

[a] Intent-to-treat population using last observation in study prior to glycaemic rescue therapy.

[b] $p < 0.05$.

[c] Not applicable.

[d] $p < 0.001$.

Canagliflozin as initial combination therapy with metformin

Canagliflozin was evaluated in combination with metformin as initial combination therapy in patients with type 2 diabetes failing diet and exercise. 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 8).

Table 8: Results from 26-week active-controlled clinical study of 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) †		-0.06‡ (-0.26, 0.13)	-0.11‡ (-0.31, 0.08)	-0.46‡ (-0.66, -0.27)	-0.48‡ (-0.67, -0.28)
Percent of patients achieving HbA_{1c} < 7%	43	39	43	50§§	57§§
Body weight					
Baseline (mean) in kg	92.1	90.3	93.0	88.3	91.5
% change from baseline (adjusted mean)	-2.1	-3.0	-3.9	-3.5	-4.2

Difference from metformin XR (adjusted mean) (95% CI)†		-0.9§§ (-1.6, -0.2)	-1.8§ (-2.6, -1.1)	-1.4‡ (-2.1, -0.6)	-2.1‡ (-2.9, -1.4)

* Intent-to-treat population

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

‡ Adjusted p = 0.001

§ Adjusted p < 0.01

§§ Adjusted p < 0.05

Special populations

In three studies conducted in special populations (elderly patients, patients with an eGFR of 30 mL/min/1.73 m^2 to < 50 mL/min/1.73 m^2 and patients with or at high risk for cardiovascular disease), canagliflozin was added to patients' current stable diabetes treatments (diet, monotherapy, or combination therapy).

Elderly

A total of 714 patients ≥ 55 years of age to ≤ 80 years of age (227 patients 65 years of age to < 75 years of age and 46 patients 75 years of age to ≤ 80 years of age) with inadequate glycaemic control on current diabetes treatment (glucose-lowering medicinal products and/or diet and exercise) participated in a double-blind, placebo-controlled study over 26 weeks. Statistically significant (p < 0.001) changes from baseline HbA_{1c} relative to placebo of -0.57% and -0.70% were observed for 100 mg once daily and 300 mg once daily, respectively (see sections 4.2 and 4.8).

Patients with eGFR 45 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2

In a pooled analysis of patients (N = 721) with a baseline eGFR 45 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2, canagliflozin provided clinically meaningful reduction in HbA_{1c} compared to placebo, with -0.47% for canagliflozin 100 mg and -0.52% for canagliflozin 300 mg. Patients with a baseline eGFR 45 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2 treated with canagliflozin 100 mg and 300 mg exhibited mean improvements in percent change in body weight relative to placebo of -1.8% and -2.0%, respectively.

The majority of patients with a baseline eGFR 45 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2 were on insulin and/or a sulphonylurea (85% [614/721]). Consistent with the expected increase of hypoglycaemia when a medicinal product not associated with hypoglycaemia is added to insulin and/or sulphonylurea, an increase in hypoglycaemia episodes/events was seen when canagliflozin was added to insulin and/or a sulphonylurea (see section 4.8).

Fasting plasma glucose

In four placebo-controlled studies, treatment with canagliflozin as monotherapy or add-on therapy with one or two oral glucose-lowering medicinal products resulted in mean changes from baseline relative to placebo in FPG of -1.2 mmol/L to -1.9 mmol/L for canagliflozin 100 mg once daily and -1.9 mmol/L to -2.4 mmol/L for canagliflozin 300 mg once daily, respectively. These reductions were sustained over the treatment period and near maximal after the first day of treatment.

Postprandial glucose

Using a mixed-meal challenge, canagliflozin as monotherapy or add-on therapy with one or two oral glucose-lowering medicinal products reduced postprandial glucose from baseline relative to placebo by -1.5 mmol/L to -2.7 mmol/L for canagliflozin 100 mg once daily and -2.1 mmol/L to -3.5 mmol/L for canagliflozin 300 mg once daily, respectively, due to reductions in the pre-meal glucose concentration and reduced postprandial glucose excursions.

Body weight

Canagliflozin 100 mg and 300 mg once daily in dual or triple add-on therapy with metformin resulted in statistically significant reductions in the percentage of body weight at 26 weeks relative to placebo. In two 52-week active-controlled studies comparing canagliflozin to glimepiride and sitagliptin, sustained and statistically significant mean reductions in the percentage of body weight for canagliflozin as add-on therapy to metformin were -4.2% and -4.7% for canagliflozin 100 mg and 300 mg once daily, respectively, compared to the combination of glimepiride and metformin (1.0%) and -2.5% for canagliflozin 300 mg once daily in combination with metformin and a sulphonylurea compared to sitagliptin in combination with metformin and a sulphonylurea (0.3%).

A subset of patients (N = 208) from the active-controlled dual therapy study with metformin who underwent dual energy X-ray densitometry (DXA) and abdominal computed tomography (CT) scans for evaluation of body composition demonstrated that approximately two-thirds of the weight loss with canagliflozin was due to loss of fat mass with similar amounts of visceral and abdominal subcutaneous fat being lost. 211 patients from the clinical study in older patients participated in a body composition substudy using DXA body composition analysis. This demonstrated that approximately two-thirds of the weight loss associated with canagliflozin was due to loss of fat mass relative to placebo. There were no meaningful changes in bone density in trabecular and cortical regions.

Blood pressure

In placebo-controlled studies, treatment with canagliflozin 100 mg and 300 mg resulted in mean reductions in systolic blood pressure of -3.9 mmHg and -5.3 mmHg, respectively, compared to placebo (-0.1 mmHg) and a smaller effect on diastolic blood pressure with mean changes for canagliflozin 100 mg and 300 mg of -2.1 mmHg and -2.5 mmHg, respectively, compared to placebo (-0.3 mmHg). There was no notable change in heart rate.

Patients with baseline HbA_{1c} > 10% to ≤ 12%

A substudy of patients with baseline HbA_{1c} > 10% to ≤ 12% with canagliflozin as monotherapy resulted in reductions from baseline in HbA_{1c} (not placebo-adjusted) of -2.13% and -2.56% for canagliflozin 100 mg and 300 mg, respectively.

Cardiovascular outcomes in the CANVAS Program

The effect of canagliflozin on cardiovascular events in adults with type 2 diabetes who had established cardiovascular (CV) disease or were at risk for CVD (two or more CV risk factors), was evaluated in the CANVAS Program (integrated analysis of the CANVAS and the CANVAS-R study). These studies were multi-centre, multi-national, randomised, double-blind, parallel group, with similar inclusion and exclusion criteria and patient populations. The CANVAS Program compared the risk of experiencing a Major Adverse Cardiovascular Event (MACE) defined as the composite of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke, between canagliflozin and placebo on a background of standard of care treatments for diabetes and atherosclerotic cardiovascular disease.

In CANVAS, subjects were randomly assigned 1:1:1 to canagliflozin 100 mg, canagliflozin 300 mg, or matching placebo. In CANVAS-R, subjects were randomly assigned 1:1 to canagliflozin 100 mg or matching placebo, and titration to 300 mg was permitted (based on tolerability and glycaemic needs) after Week 13. Concomitant antidiabetic and atherosclerotic therapies could be adjusted, according to the standard care for these diseases.

A total of 10,134 patients were treated (4,327 in CANVAS and 5,807 in CANVAS-R; total of 4,344 randomly assigned to placebo and 5,790 to canagliflozin) for a mean exposure duration of 149 weeks (223 weeks in CANVAS and 94 weeks in CANVAS-R). Vital status was obtained for 99.6% of subjects across the studies. The mean age was 63 years and 64% were male. Sixty-six percent of subjects had a history of established cardiovascular disease, with 56% having a history of coronary

disease, 19% with cerebrovascular disease, and 21% with peripheral vascular disease; 14% had a history of heart failure.

The mean HbA_{1c} at baseline was 8.2% and mean duration of diabetes was 13.5 years.

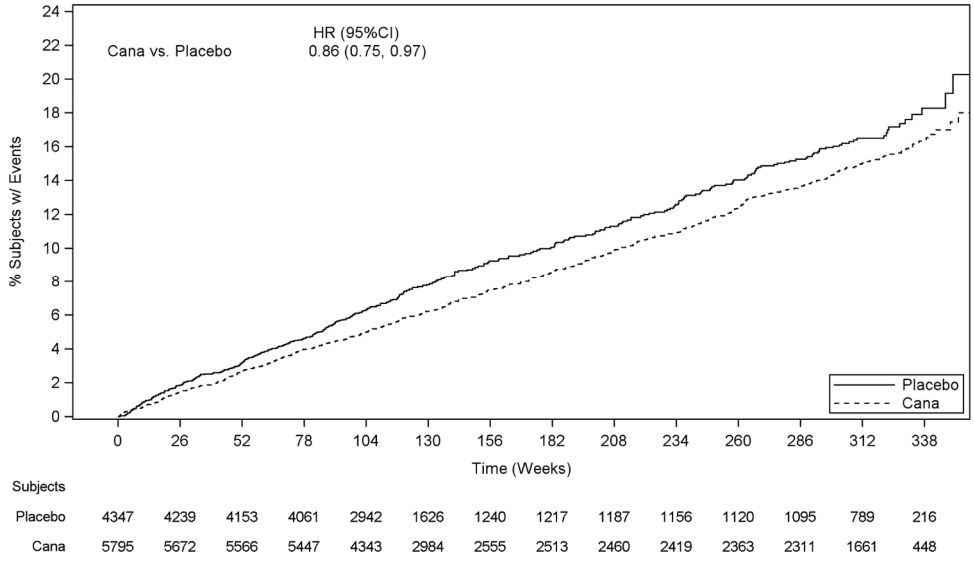
Baseline renal function was normal or mildly impaired in 80% of patients and moderately impaired in 20% of patients (mean eGFR 77 mL/min/1.73 m^2). At baseline, patients were treated with one or more antidiabetic medicinal products including metformin (77%), insulin (50%), and sulfonylurea (43%).

The primary endpoint in the CANVAS Program was the time to first occurrence of a MACE. Secondary endpoints within a sequential conditional hypothesis testing were all-cause mortality and cardiovascular mortality.

Patients in the pooled canagliflozin groups (pooled analysis of canagliflozin 100 mg, canagliflozin 300 mg, and canagliflozin up-titrated from 100 mg to 300 mg) had a lower rate of MACE as compared to placebo: 2.69 *versus* 3.15 patients per 100 patient-years (HR of the pooled analysis: 0.86; 95% CI (0.75, 0.97).

Based on the Kaplan-Meier plot for the first occurrence of MACE, shown below, the reduction in MACE in the canagliflozin group was observed as early as Week 26 and was maintained throughout the remainder of the study (see Figure 1).

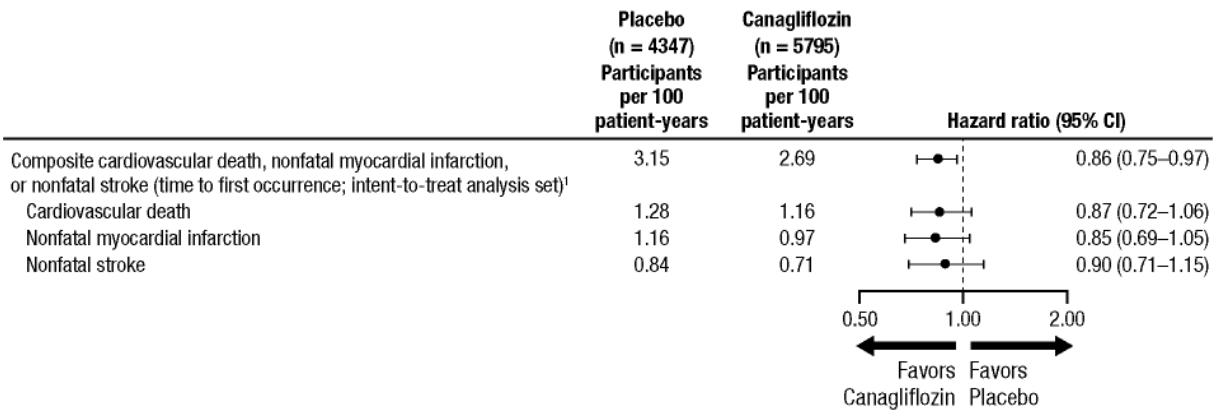
Figure 1: Time to first occurrence of MACE



There were 2,011 patients with eGFR 30 to < 60 mL/min/1.73 m^2. The MACE findings in this subgroup were consistent with the overall findings.

Each MACE component positively contributed to the overall composite, as shown in Figure 2. Results for the 100 mg and 300 mg canagliflozin doses were consistent with results for the combined dose groups.

Figure 2: Treatment effect for the primary composite endpoint and its components



1 P value for superiority (2-sided) = 0.0158.

All-cause mortality

In the combined canagliflozin group, the HR for all-cause mortality versus placebo was 0.87 (0.74, 1.01).

Heart failure requiring hospitalisation

Canagliflozin reduced the risk for heart failure requiring hospitalisation compared to placebo (HR: 0.67; 95% CI (0.52, 0.87)).

Renal endpoints

In the CANVAS Program, for time to first adjudicated nephropathy event (doubling of serum creatinine, need for renal-replacement therapy, and renal death), the HR was 0.53 (95% CI: 0.33, 0.84) for canagliflozin (0.15 events per 100 patient-years) versus placebo (0.28 events per 100 patient-years). In addition, canagliflozin reduced progression of albuminuria 25.8% versus placebo 29.2% (HR: 0.73; 95% CI: 0.67, 0.79) in patients with baseline normo- or micro-albuminuria.

Canagliflozin 100 mg has also been studied in adults with type 2 diabetes and diabetic kidney disease with estimated glomerular filtration rate (eGFR) 30 to < 90 mL/min/1.73 m^2 and albuminuria (> 33.9 to 565.6 mg/mmol of creatinine). No information in this patient population is available for the canagliflozin/metformin fixed dose combination.

Metformin

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with metformin after failure of diet alone showed:

- a significant reduction of the absolute risk of any diabetesrelated complication in the metformin group (29.8 events/1,000 patient-years) *versus* diet alone (43.3 events/1,000 patient-years), p = 0.0023, and *versus* the combined sulphonylurea and insulin monotherapy groups (40.1 events/1,000 patient-years), p = 0.0034
- a significant reduction of the absolute risk of any diabetes-related mortality: metformin 7.5 events/1,000 patient-years, diet alone 12.7 events/1,000 patient-years, p = 0.017
- a significant reduction of the absolute risk of overall mortality: metformin 13.5 events/1,000 patient-years *versus* diet alone 20.6 events/1,000 patient-years, (p = 0.011), and *versus* the combined sulphonylurea and insulin monotherapy groups 18.9 events/1,000 patient-years (p = 0.021)
- a significant reduction in the absolute risk of myocardial infarction: metformin 11 events/1,000 patient-years, diet alone 18 events/1,000 patient-years, (p = 0.01).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Vokanamet in all subsets of the paediatric population in type 2 diabetes (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Vokanamet

Bioequivalence studies in healthy subjects demonstrated that Vokanamet 50 mg/850 mg, 50 mg/1,000 mg, 150 mg/850 mg, and 150 mg/1,000 mg combination tablets are bioequivalent to co-administration of corresponding doses of canagliflozin and metformin as individual tablets.

Administration of Vokanamet 150 mg/1,000 mg with food resulted in no change in overall exposure of canagliflozin. There was no change in metformin AUC; however, 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 (2 hours for canagliflozin and 1 hour for metformin) under fed conditions. These changes are not likely to be clinically relevant. As metformin is recommended to be administered with a meal to reduce the incidence of gastrointestinal adverse reactions, it is recommended that Vokanamet be taken with a meal to reduce gastrointestinal intolerability associated with metformin.

Canagliflozin

The pharmacokinetics of canagliflozin are essentially similar in healthy subjects and patients with type 2 diabetes. After single-dose oral administration of 100 mg and 300 mg in healthy subjects, canagliflozin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1 hour 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 ($t_{1/2}$) (expressed as mean ± standard deviation) was 10.6 ± 2.13 hours and 13.1 ± 3.28 hours for the 100 mg and 300 mg doses, respectively. Steady-state was reached after 4 days 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.

Absorption

The mean absolute oral bioavailability of canagliflozin is approximately 65%. Co-administration of a high-fat meal with canagliflozin had no effect on the pharmacokinetics of canagliflozin; therefore, canagliflozin may be taken with or without food (see section 4.2).

Distribution

The mean steady-state volume of distribution (V_d) of canagliflozin following a single intravenous infusion in healthy subjects was 83.5 litres, 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.

Biotransformation

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.

In *in vitro* studies, canagliflozin neither inhibited cytochrome P450 CYP1A2, CYP2A6, CYP2C19, CYP2D6, or CYP2E1, CYP2B6, CYP2C8, CYP2C9, nor induced CYP1A2, CYP2C19, CYP2B6,

CYP3A4 at higher than therapeutic concentrations. No clinically relevant effect on CYP3A4 was observed *in vivo* (see section 4.5).

Elimination

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 faeces 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 mL/min to 1.55 mL/min.

Canagliflozin is a low-clearance substance, with a mean systemic clearance of approximately 192 mL/min in healthy subjects following intravenous administration.

Special populations

Renal impairment
A single-dose, open-label study evaluated the pharmacokinetics of canagliflozin 200 mg in subjects with varying degrees of renal impairment (classified using CrCl based on the Cockroft-Gault equation) compared to healthy subjects. The study included 8 subjects with normal renal function (CrCl ≥ 80 mL/min), 8 subjects with mild renal impairment (CrCl 50 mL/min to < 80 mL/min), 8 subjects with moderate renal impairment (CrCl 30 mL/min to < 50 mL/min), and 8 subjects with severe renal impairment (CrCl < 30 mL/min) as well as 8 subjects with end-stage kidney disease (ESKD) on haemodialysis.

The C_{max} of canagliflozin was moderately increased by 13%, 29%, and 29% in subjects with mild, moderate, and severe renal failure, respectively, but not in subjects on haemodialysis. Compared to healthy subjects, plasma AUC of canagliflozin was increased by approximately 17%, 63%, and 50% in subjects with mild, moderate, and severe renal impairment, respectively, but was similar for ESKD subjects and healthy subjects.

Canagliflozin was negligibly removed by haemodialysis.

Hepatic impairment
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.

Elderly
Age had no clinically meaningful effect on the pharmacokinetics of canagliflozin based on a population pharmacokinetic analysis (see sections 4.2, 4.4, and 4.8).

Paediatric population
A paediatric phase 1 study examined the pharmacokinetics and pharmacodynamics of canagliflozin in children and adolescents ≥ 10 to < 18 years of age with type 2 diabetes mellitus. The observed pharmacokinetic and pharmacodynamic responses were consistent with those found in adult subjects.

Other special populations

Pharmacogenetics

Both UGT1A9 and UGT2B4 are subject to genetic polymorphism. In a pooled analysis of clinical data, increases in canagliflozin AUC of 26% were observed in UGT1A9*1/*3 carriers and 18% in UGT2B4*2/*2 carriers. These increases in canagliflozin exposure are not expected to be clinically relevant. The effect of being homozygote (UGT1A9*3/*3, frequency < 0.1%) is probably more marked, but has not been investigated.

Gender, race/ethnicity, or body mass index had no clinically meaningful effect on the pharmacokinetics of canagliflozin based on a population pharmacokinetic analysis.

Metformin

Absorption

After an oral dose of metformin hydrochloride tablet, C_{max} is reached in approximately 2.5 hours (T_{max}). Absolute bioavailability of a 500 mg or 850 mg metformin hydrochloride tablet is approximately 50-60% in healthy subjects. After an oral dose, the non-absorbed fraction recovered in faeces was 20-30%.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption are non-linear.

At the recommended metformin doses and dosing schedules, steady-state plasma concentrations are reached within 24-48 hours and are generally less than 1 μg/mL. In controlled clinical studies, C_{max} did not exceed 5 μg/mL, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin. Following oral administration of an 850 mg tablet, a 40% lower plasma peak concentration, a 25% decrease in AUC, and a 35-minute prolongation of time to peak plasma concentration were observed. The clinical relevance of these findings is unknown.

Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean V_d ranged between 63–276 litres.

Biotransformation

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination

Renal clearance of metformin is > 400 mL/min, indicating that metformin hydrochloride is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 hours.

When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

Paediatric population

Single dose study: After single doses of metformin hydrochloride 500 mg, paediatric patients have shown a similar pharmacokinetic profile to that observed in healthy adults.

Multiple dose study: Data are restricted to one study. After repeated doses of 500 mg twice daily for 7 days in paediatric patients, the peak C_{max} and AUC_{0-t} were reduced by approximately 33% and 40%, respectively compared to diabetic adults who received repeated doses of 500 mg twice daily for

14 days. As the dose is individually titrated based on glycaemic control, this is of limited clinical relevance.

5.3 Preclinical safety data

Canagliflozin

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and genotoxicity.

Canagliflozin showed no effects on fertility and early embryonic development in the rat at exposures up to 19 times the human exposure at the maximum recommended human dose (MRHD).

In an embryo-foetal development study in rats, ossification delays of metatarsal bones were observed at systemic exposures 73 times and 19 times higher than the clinical exposures at the 100 mg and 300 mg doses. It is unknown whether ossification delays can be attributed to effects of canagliflozin on calcium homeostasis observed in adult rats.

In a pre- and postnatal development study, canagliflozin administered to female rats from gestation day 6 to lactation day 20 resulted in decreased body weights in male and female offspring at maternally toxic doses > 30 mg/kg/day (exposures ≥ 5.9 times the human exposure to canagliflozin at the MHRD). Maternal toxicity was limited to decreased body weight gain.

A study in juvenile rats administered canagliflozin from day 21 through day 90 postnatal did not show increased sensitivity compared to effects observed in adults rats. However, dilatation of the renal pelvis was noticed with a No Observed Effect Level (NOEL) at exposures 2.4 times and 0.5 times the clinical exposures at 100 mg and 300 mg doses, respectively, and did not fully reverse within the approximately 1-month recovery period. Persistent renal findings in juvenile rats can most likely be attributed to reduced ability of the developing rat kidney to handle canagliflozin-increased urine volumes, as functional maturation of the rat kidney continues through 6 weeks of age.

Canagliflozin did not increase the incidence of tumours in male and female mice in a 2-year study at doses of 10, 30, and 100 mg/kg. The highest dose of 100 mg/kg provided up to 14 times the clinical dose of 300 mg based on AUC exposure. Canagliflozin increased the incidence of testicular Leydig cell tumours in male rats at all doses tested (10, 30, and 100 mg/kg); the lowest dose of 10 mg/kg is approximately 1.5 times the clinical dose of 300 mg based on AUC exposure. The higher doses of canagliflozin (100 mg/kg) in male and female rats increased the incidence of pheochromocytomas and renal tubular tumours. Based on AUC exposure, the NOEL of 30 mg/kg/day for pheochromocytomas and renal tubular tumours is approximately 4.5 times the exposure at the daily clinical dose of 300 mg. Based on preclinical and clinical mechanistic studies, Leydig cell tumours, renal tubule tumours and pheochromocytomas are considered to be rat-specific. Canagliflozin-induced renal tubule tumours and pheochromocytomas in rats appear to be caused by carbohydrate malabsorption as a consequence of intestinal SGLT1 inhibitory activity of canagliflozin in the gut of rats; mechanistic clinical studies have not demonstrated carbohydrate malabsorption in humans at canagliflozin doses of up to 2-times the maximum recommended clinical dose. The Leydig cell tumours are associated with an increase in luteinising hormone (LH), which is a known mechanism of Leydig cell tumour formation in rats. In a 12-week clinical study, unstimulated LH did not increase in male patients treated with canagliflozin.

Metformin

Preclinical data reveal no special hazard for humans based on conventional studies on safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and fertility.

Environmental Risk Assessment: no environmental impact is anticipated from the clinical use of either of the active substances canagliflozin or metformin in Vokanamet.

Canagliflozin/metformin

In a study on embryo-foetal development in rats, metformin alone (300 mg/kg/day) caused absent/incomplete ossification, while canagliflozin alone (60 mg/kg/day) had no effects. When canagliflozin/metformin was administered at 60/300 mg/kg/day (exposure levels 11 and 13 times the clinical exposure for canagliflozin and metformin, respectively, at 300/2,000 mg doses), the effects were more pronounced compared to metformin alone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose
Hypromellose
Croscarmellose sodium
Magnesium stearate

Film-coating

Vokanamet 50 mg/850 mg film-coated tablets

Macrogol (3350)
Poly(vinyl alcohol)
Talc
Titanium dioxide (E171)
Iron oxide red (E172)
Iron oxide black (E172)

Vokanamet 50 mg/1,000 mg film-coated tablets

Macrogol (3350)
Poly(vinyl alcohol)
Talc
Titanium dioxide (E171)
Iron oxide red (E172)
Iron oxide yellow (E172)

Vokanamet 150 mg/850 mg film-coated tablets

Macrogol (3350)
Poly(vinyl alcohol)
Talc
Titanium dioxide (E171)
Iron oxide yellow (E172)

Vokanamet 150 mg/1,000 mg film-coated tablets

Macrogol (3350)
Poly(vinyl alcohol)
Talc
Titanium dioxide (E171)
Iron oxide red (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

HDPE bottle with child-resistant closure, induction seal, and desiccant.
The bottles contain 20 or 60 film-coated tablets.

Pack sizes:
1 x 20 film-coated tablets
1 x 60 film-coated tablets
Multipack containing 180 (3 x 60) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

Vokanamet 50 mg/850 mg film-coated tablets

EU/1/14/918/001 (20 film-coated tablets)
EU/1/14/918/002 (60 film-coated tablets)
EU/1/14/918/003 (180 film-coated tablets)

Vokanamet 50 mg/1,000 mg film-coated tablets

EU/1/14/918/004 (20 film-coated tablets)
EU/1/14/918/005 (60 film-coated tablets)
EU/1/14/918/006 (180 film-coated tablets)

Vokanamet 150 mg/850 mg film-coated tablets

EU/1/14/918/007 (20 film-coated tablets)
EU/1/14/918/008 (60 film-coated tablets)
EU/1/14/918/009 (180 film-coated tablets)

Vokanamet 150 mg/1,000 mg film-coated tablets

EU/1/14/918/010 (20 film-coated tablets)
EU/1/14/918/011 (60 film-coated tablets)
EU/1/14/918/012 (180 film-coated tablets)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 April 2014
Date of latest renewal: 18 December 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Janssen-Cilag SpA
Via C. Janssen
Borgo San Michele
04100 Latina
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Vokanamet 50 mg/850 mg film-coated tablets
Vokanamet 50 mg/1,000 mg film-coated tablets
Vokanamet 150 mg/850 mg film-coated tablets
Vokanamet 150 mg/1,000 mg film-coated tablets
canagliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains canagliflozin hemihydrate, equivalent to 50 mg canagliflozin, and 850 mg metformin hydrochloride.
Each tablet contains canagliflozin hemihydrate, equivalent to 50 mg canagliflozin, and 1,000 mg metformin hydrochloride.
Each tablet contains canagliflozin hemihydrate, equivalent to 150 mg canagliflozin, and 850 mg metformin hydrochloride.
Each tablet contains canagliflozin hemihydrate, equivalent to 150 mg canagliflozin, and 1,000 mg metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
20 film-coated tablets
60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/918/001 (50 mg/850 mg – 20 film-coated tablets)
EU/1/14/918/002 (50 mg/850 mg – 60 film-coated tablets)

EU/1/14/918/004 (50 mg/1,000 mg – 20 film-coated tablets)
EU/1/14/918/005 (50 mg/1,000 mg – 60 film-coated tablets)

EU/1/14/918/007 (150 mg/850 mg – 20 film-coated tablets)
EU/1/14/918/008 (150 mg/850 mg – 60 film-coated tablets)

EU/1/14/918/010 (150 mg/1,000 mg – 20 film-coated tablets)
EU/1/14/918/011 (150 mg/1,000 mg – 60 film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

vokanamet 50 mg/850 mg
vokanamet 50 mg/1,000 mg
vokanamet 150 mg/850 mg
vokanamet 150 mg/1,000 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Vokanamet 50 mg/850 mg film-coated tablets
Vokanamet 50 mg/1,000 mg film-coated tablets
Vokanamet 150 mg/850 mg film-coated tablets
Vokanamet 150 mg/1,000 mg film-coated tablets
canagliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains canagliflozin hemihydrate, equivalent to 50 mg canagliflozin, and 850 mg metformin hydrochloride.
Each tablet contains canagliflozin hemihydrate, equivalent to 50 mg canagliflozin, and 1,000 mg metformin hydrochloride.
Each tablet contains canagliflozin hemihydrate, equivalent to 150 mg canagliflozin, and 850 mg metformin hydrochloride.
Each tablet contains canagliflozin hemihydrate, equivalent to 150 mg canagliflozin, and 1,000 mg metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
20 film-coated tablets
60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/918/001 (50 mg/850 mg – 20 film-coated tablets)
EU/1/14/918/002 (50 mg/850 mg – 60 film-coated tablets)

EU/1/14/918/004 (50 mg/1,000 mg – 20 film-coated tablets)
EU/1/14/918/005 (50 mg/1,000 mg – 60 film-coated tablets)

EU/1/14/918/007 (150 mg/850 mg – 20 film-coated tablets)
EU/1/14/918/008 (150 mg/850 mg – 60 film-coated tablets)

EU/1/14/918/010 (150 mg/1,000 mg – 20 film-coated tablets)
EU/1/14/918/011 (150 mg/1,000 mg – 60 film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

LABEL FOR MULTIPACK COMPRISING 3 PACKS (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Vokanamet 50 mg/850 mg film-coated tablets
Vokanamet 50 mg/1,000 mg film-coated tablets
Vokanamet 150 mg/850 mg film-coated tablets
Vokanamet 150 mg/1,000 mg film-coated tablets
canagliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains canagliflozin hemihydrate, equivalent to 50 mg canagliflozin, and 850 mg metformin hydrochloride.
Each tablet contains canagliflozin hemihydrate, equivalent to 50 mg canagliflozin, and 1,000 mg metformin hydrochloride.
Each tablet contains canagliflozin hemihydrate, equivalent to 150 mg canagliflozin, and 850 mg metformin hydrochloride.
Each tablet contains canagliflozin hemihydrate, equivalent to 150 mg canagliflozin, and 1,000 mg metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
Multipack: 180 (3 packs of 60) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/918/003 (50 mg/850 mg – 180 film-coated tablets)
EU/1/14/918/006 (50 mg/1,000 mg – 180 film-coated tablets)
EU/1/14/918/009 (150 mg/850 mg – 180 film-coated tablets)
EU/1/14/918/012 (150 mg/1,000 mg – 180 film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

vokanamet 50 mg/850 mg
vokanamet 50 mg/1,000 mg
vokanamet 150 mg/850 mg
vokanamet 150 mg/1,000 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR 1 COMPONENT OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Vokanamet 50 mg/850 mg film-coated tablets
Vokanamet 50 mg/1,000 mg film-coated tablets
Vokanamet 150 mg/850 mg film-coated tablets
Vokanamet 150 mg/1,000 mg film-coated tablets
canagliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains canagliflozin hemihydrate, equivalent to 50 mg canagliflozin, and 850 mg metformin hydrochloride.
Each tablet contains canagliflozin hemihydrate, equivalent to 50 mg canagliflozin, and 1,000 mg metformin hydrochloride.
Each tablet contains canagliflozin hemihydrate, equivalent to 150 mg canagliflozin, and 850 mg metformin hydrochloride.
Each tablet contains canagliflozin hemihydrate, equivalent to 150 mg canagliflozin, and 1,000 mg metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
60 film-coated tablets. Component of a 3 bottle multipack, can not be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/918/003 (50 mg/850 mg – 180 film-coated tablets)
EU/1/14/918/006 (50 mg/1,000 mg – 180 film-coated tablets)
EU/1/14/918/009 (150 mg/850 mg – 180 film-coated tablets)
EU/1/14/918/012 (150 mg/1,000 mg – 180 film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

vokanamet 50 mg/850 mg
vokanamet 50 mg/1,000 mg
vokanamet 150 mg/850 mg
vokanamet 150 mg/1,000 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL COMPONENT OF MULTIPACK

1. NAME OF THE MEDICINAL PRODUCT

Vokanamet 50 mg/850 mg film-coated tablets
Vokanamet 50 mg/1,000 mg film-coated tablets
Vokanamet 150 mg/850 mg film-coated tablets
Vokanamet 150 mg/1,000 mg film-coated tablets
canagliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains canagliflozin hemihydrate, equivalent to 50 mg canagliflozin, and 850 mg metformin hydrochloride.
Each tablet contains canagliflozin hemihydrate, equivalent to 50 mg canagliflozin, and 1,000 mg metformin hydrochloride.
Each tablet contains canagliflozin hemihydrate, equivalent to 150 mg canagliflozin, and 850 mg metformin hydrochloride.
Each tablet contains canagliflozin hemihydrate, equivalent to 150 mg canagliflozin, and 1,000 mg metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
60 film-coated tablets
Component of a 3 bottle multipack, can not be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/918/003 (50 mg/850 mg – 180 film-coated tablets)
EU/1/14/918/006 (50 mg/1,000 mg – 180 film-coated tablets)
EU/1/14/918/009 (150 mg/850 mg – 180 film-coated tablets)
EU/1/14/918/012 (150 mg/1,000 mg – 180 film-coated tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Vokanamet 50 mg/850 mg film-coated tablets
Vokanamet 50 mg/1,000 mg film-coated tablets
Vokanamet 150 mg/850 mg film-coated tablets
Vokanamet 150 mg/1,000 mg film-coated tablets

canagliflozin/metformin hydrochloride

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Vokanamet is and what it is used for

Vokanamet contains two different active substances, canagliflozin and metformin. These are two medicines that work together in different ways to lower blood glucose (sugar) levels and can help prevent heart disease in adults with type 2 diabetes.

This medicine can be used by itself or along with other medicines you may be using to treat your type 2 diabetes (such as insulin, a DPP-4 inhibitor [such as sitagliptin, saxagliptin, or linagliptin], a sulphonylurea [such as glimepiride or glipizide], or pioglitazone) that lower blood sugar levels. You may already be taking one or more of these to treat your type 2 diabetes. Vokanamet is used when your blood sugar cannot be adequately controlled by metformin alone or together with other diabetes medicines. If you are already taking both canagliflozin and metformin as single tablets, Vokanamet can replace them in one tablet.

It is important to keep following advice about diet and exercise given by your doctor or nurse.

What is type 2 diabetes?
Type 2 diabetes is a condition in which your body does not make enough insulin, and the insulin that your body produces does not work as well as it should. Your body can also make too much sugar. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical conditions such as heart disease, kidney disease, blindness, and amputation.

2. What you need to know before you take Vokanamet

Do not take Vokanamet
- if you are allergic to canagliflozin, metformin or any of the other ingredients of this medicine (listed in section 6)
- if you have liver problems
- if you have severely reduced kidney function

- if you have uncontrolled diabetes, with, for example,severe hyperglycaemia (high blood glucose), nausea, vomiting, diarrhoea, rapid weight loss, lactic acidosis (see “Risk of lactic acidosis” below) or ketoacidosis. Ketoacidosis is a condition in which substances called 'ketone bodies' accumulate in the blood and which can lead to diabetic pre-coma. Symptoms include stomach pain, fast and deep breathing, sleepiness or your breath developing an unusual fruity smell.
- if you have a severe infection
- if you have lost a lot of water from your body (dehydration), e.g. due to long-lasting or severe diarrhoea, or if you have vomited several times in a row
- if you have a diabetic pre-coma
- if you have recently had a heart attack or have severe blood circulation problems, such as ‘shock’ or breathing difficulties
- if you drink alcohol to excess (either every day or from time to time)
- if you have or have recently had heart failure.

Warnings and precautions
Risk of lactic acidosis
Vokanamet may cause a very rare, but very serious side effect called lactic acidosis, particularly if your kidneys are not working properly. The risk of developing lactic acidosis is also increased with uncontrolled diabetes, serious infections, prolonged fasting or alcohol intake, dehydration (see further information below), liver problems and any medical conditions in which a part of the body has a reduced supply of oxygen (such as acute severe heart disease).
If any of the above applies to you, talk to your doctor for further instructions.

Talk to your doctor promptly for further instructions if:
- You are known to suffer from a genetically inherited disease affecting mitochondria (the energy-producing components within cells) such as MELAS syndrome (Mitochondrial Encephalopathy, Lactic acidosis and Stroke-like episodes) or Maternal inherited diabetes and deafness (MIDD).
- You have any of these symptoms after starting metformin: seizure, declined cognitive abilities, difficulty with body movements, symptoms indicating nerve damage (e.g. pain or numbness), migraine and deafness.

Temporarily stop taking Vokanamet if you have a condition that may be associated with dehydration (significant loss of body fluids) such as severe vomiting, diarrhoea, fever, exposure to heat or if you drink less fluid than normal. Talk to your doctor for further instructions.

Stop taking Vokanamet and talk to a doctor or go to the nearest hospital immediately if you experience some of the symptoms of lactic acidosis, as this condition may lead to coma.
Symptoms of lactic acidosis include:
- vomiting
- stomach ache (abdominal pain)
- muscle cramps
- a general feeling of not being well with severe tiredness
- difficulty in breathing
- reduced body temperature and heartbeat

Lactic acidosis is a medical emergency and must be treated in a hospital.

Talk to your doctor, pharmacist or nurse before taking Vokanamet, and during treatment:
- about what you can do to prevent dehydration (see section 4 for signs of dehydration).
- if you have type 1 diabetes because Vokanamet should not be used to treat this condition.
- if you experience rapid weight loss, feeling sick or being sick, stomach pain, excessive thirst, fast and deep breathing, confusion, unusual sleepiness or tiredness, a sweet smell to your breath, a sweet or metallic taste in your mouth or a different odour to your urine or sweat,talk to a doctor or go to the nearest hospital immediately. These symptoms could be a sign of “diabetic

ketoacidosis" – a rare but serious, sometimes life-threatening problem you can get with diabetes because of increased levels of "ketone bodies" in your urine or blood, seen in tests. The risk of developing diabetic ketoacidosis may be increased with prolonged fasting, excessive alcohol consumption, dehydration, sudden reductions in insulin dose, or a higher need of insulin due to major surgery or serious illness.

- if you are going to have major surgery or a procedure that requires prolonged fasting, ask your doctor if you need to stop taking Vokanamet and when to start it again.
- if you have ever had serious heart disease or if you have had a stroke.
- if you are on medicines to lower your blood pressure (anti-hypertensives) or have ever had low blood pressure (hypotension). More information is given below in "Other medicines and Vokanamet".
- if you have had a lower limb amputation.
- It is important to check your feet regularly and adhere to any other advice regarding foot care and adequate hydration given by your healthcare professional. You should notify your doctor immediately if you notice any wounds or discolouration, or if you experience any tenderness or pain in your feet. Some studies indicate that taking canagliflozin may have contributed to the risk of lower limb amputation (mainly toe and midfoot amputations).
- Talk to your doctor immediately if you develop a combination of symptoms of pain, tenderness, redness, or swelling of the genitals or the area between the genitals and the anus with fever or feeling generally unwell. These symptoms could be a sign of a rare but serious or even life-threatening infection, called necrotising fasciitis of the perineum or Fournier's gangrene which destroys the tissue under the skin. Fournier's gangrene has to be treated immediately.
- if you have signs of a genital yeast infection such as irritation, itching, unusual discharge or odour
- if you have a serious infection of the kidney or the urinary tract with fever. Your doctor may ask you to stop taking Vokanamet until you have recovered.

Kidney function
Your kidneys will be tested by a blood test before you start taking and during treatment with Vokanamet. Your doctor will check your kidney function at least once a year or more frequently if you are elderly and/or if you have worsening kidney function.

Surgery
If you need to have major surgery you must stop taking Vokanamet during and for some time after the procedure. Your doctor will decide when you must stop and when to restart your treatment with Vokanamet.

Your doctor will decide whether you need any other treatment to control your blood sugar while you have stopped taking Vokanamet. It is important that you follow your doctor's instructions carefully.

Urine glucose
Because of the way canagliflozin works, your urine will test positive for sugar (glucose) while you are taking this medicine.

Children and adolescents
Vokanamet is not recommended for children and adolescents under 18 years, because data are not available in these patients.

Other medicines and Vokanamet
If you need to have an injection of a contrast medium that contains iodine into your bloodstream, for example in the context of an X-ray or scan, you must stop taking Vokanamet before or at the time of the injection. Your doctor will decide when you must stop and when to restart your treament with Vokanamet.

Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines. This is because this medicine can affect the way some other medicines work. Also, some other medicines can affect the way this medicine works. You may need more frequent blood glucose

and kidney function tests, or your doctor may need to adjust the dose of Vokanamet. It is especially important to mention the following:

- insulin or a sulphonylurea (such as glimepiride or glipizide) for diabetes – your doctor may want to reduce your dose in order to avoid your blood sugar level from getting too low (hypoglycaemia)
- medicines which increase urine production (diuretics)
- St. John's wort (a herbal medicine used to treat depression)
- carbamazepine, phenytoin, or phenobarbital (medicines used to control seizures)
- lithium (a medicine used to treat bipolar disorder)
- efavirenz or ritonavir (medicines used to treat HIV infection)
- rifampicin (an antibiotic used to treat tuberculosis)
- cholestyramine (medicine used to reduce cholesterol levels in the blood). See section 3, “Taking this medicine”.
- digoxin or digitoxin (medicines used for certain heart problems). The level of digoxin or digitoxin in your blood may need to be checked if taken with Vokanamet.
- dabigatran (blood thinner medicine that lowers the risk of blood clot formation)
- medicines that contain alcohol. See section “Vokanamet with alcohol”.
- cimetidine (medicine used to treat stomach problems)
- corticosteroids (used to treat a variety of conditions, such as severe inflammation of the skin or in asthma) that are given by mouth, as an injection, or inhaled
- beta-2 agonists (such as salbutamol or terbutaline) used to treat asthma.
- medicines used to treat pain and inflammation (NSAID and COX-2-inhibitors, such as ibuprofen and celecoxib)
- certain medicines for the treatment of high blood pressure (ACE inhibitors and angiotensin II receptor antagonists)

Vokanamet with alcohol
Avoid excessive alcohol intake while taking this medicine since this may increase the risk of lactic acidosis. See section “Warning and precautions”.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking or continuing to take this medicine.

Canagliflozin, one of the ingredients in Vokanamet, should not be used during pregnancy. Talk to your doctor about the best way to control your blood sugar without Vokanamet as soon as you know that you are pregnant.

You should not take this medicine if you are breast-feeding. Talk to your doctor about whether to stop taking this medicine or to stop breast-feeding.

Driving and using machines
Vokanamet has no or negligible influence on the ability to drive, cycle, and use tools or machines. However, dizziness or lightheadedness has been reported, which may affect your ability to drive, cycle, or use tools or machines.

Taking Vokanamet with other medicines for diabetes called sulphonylureas (such as glimepiride or glipizide) or insulin can increase the risk of having low blood sugar (hypoglycaemia). Signs include blurred vision, tingling lips, trembling, sweating, pale looking, a change in mood, or feeling anxious or confused. This may affect your ability to drive, cycle, and use any tools or machines. Tell your doctor as soon as possible if you get any signs of low blood sugar.

Vokanamet contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium free’.

3. How to take Vokanamet

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How much to take
- The dose of Vokanamet is one tablet twice a day.
- The strength of Vokanamet that you will take varies depending on your condition and the amount of canagliflozin and metformin needed to control your blood sugar.
- Your doctor will prescribe the strength that is right for you.

Taking this medicine
- Swallow the tablet whole with water.
- It is best to take your tablet with a meal. This will lower your chance of having an upset stomach.
- Try to take it at the same times each day. This will help you remember to take it.
- If your doctor has prescribed this medicine along with any medicine for lowering cholesterol such as cholestyramine you should take this medicine at least 1 hour before or 4 hours to 6 hours after the cholesterol-lowering medicine.

Your doctor may prescribe Vokanamet together with another glucose-lowering medicine. Remember to take all medicines as directed by your doctor to achieve the best results for your health.

Diet and exercise
To help control your diabetes, you still need to follow the advice about diet and exercise from your doctor, pharmacist or nurse. In particular, if you are following a diabetic weight control diet, continue to follow it while you are taking this medicine.

If you take more Vokanamet than you should
As Vokanamet contains metformin, if you take more of this medicine, you may experience lactic acidosis. If this happens to you, you may need immediate hospital treatment, as lactic acidosis may lead to coma. Symptoms of lactic acidosis include vomiting, stomach ache, muscle cramps, a general feeling of not being well with severe tiredness, or difficulty breathing. Further symptoms are reduced body temperature and heartbeat. Stop taking this medicine immediately and contact a doctor or the nearest hospital straight away (see section 2). Take the medicine pack with you.

If you forget to take Vokanamet
- If you forget to take a dose, take it as soon as you remember. However, if it is time for the next dose, skip the missed dose.
- Do not take a double dose to make up for a forgotten dose.

If you stop taking Vokanamet
Your blood sugar levels may rise if you stop taking this medicine. Do not stop taking this medicine without talking to your doctor first.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking Vokanamet and talk to a doctor or go to the nearest hospital immediately if you have any of the following serious side effects:

Severe allergic reaction (rare, may affect up to 1 in 1,000 people)
Possible signs of severe allergic reaction may include:
- swelling of the face, lips, mouth, tongue, or throat that may lead to difficulty breathing or swallowing.

Lactic acidosis (very rare, may affect up to 1 in 10,000 people)
Vokanamet may cause a very rare but very serious side effect called lactic acidosis (see section "Warnings and precautions"). If this happens, you must **stop taking Vokanamet and talk to a doctor or go to the nearest hospital immediately**, as lactic acidosis may lead to coma.

Diabetic ketoacidosis (rare, may affect up to 1 in 1,000 people)
These are the signs of diabetic ketoacidosis (see also section 2):
- increased levels of "ketone bodies" in your urine or blood
- rapid weight loss
- feeling sick or being sick
- stomach pain
- excessive thirst
- fast and deep breathing
- confusion
- unusual sleepiness or tiredness
- a sweet smell to your breath, a sweet or metallic taste in your mouth or a different odour to your urine or sweat.

This may occur regardless of blood glucose level. The doctor may decide to temporarily or permanently stop the treatment with Vokanamet.

Dehydration (uncommon, may affect up to 1 in 100 people)
- loss of too much fluid from your body (dehydration). This happens more often in elderly people (aged 75 and over), people with kidney problems, and people taking water tablets (diuretics).
  Possible signs of dehydration are:
  - feeling light-headed or dizzy
  - passing out (fainting) or feeling dizzy or faint when you stand up
  - very dry or sticky mouth, feeling very thirsty
  - feeling very weak or tired
  - passing little or no urine
  - fast heartbeat.

Tell your doctor as soon as possible if you have any of the following side effects:
Hypoglycaemia (very common, may affect more than 1 in 10 people)
- low blood sugar levels (hypoglycaemia) - when taking this medicine with insulin or a sulphonylurea (such as glimepiride or glipizide).
  Possible signs of low blood sugar are:
  - blurred vision
  - tingling lips
  - trembling, sweating, looking pale
  - a change in mood or feeling anxious or confused.

Your doctor will tell you how to treat low blood sugar levels and what to do if you have any of the signs above.

Urinary tract infections (common, may affect up to 1 in 10 people)
- These are signs of a severe infection of the urinary tract, e.g.:
  - fever and/or chills
  - burning sensation when passing water (urinating)

- pain in your back or side.

Although uncommon, if you see blood in your urine, tell your doctor immediately.

Other side effects when taking canagliflozin alone:
Very common (may affect more than 1 in 10 people)
- vaginal yeast infection.

Common (may affect up to 1 in 10 people)
- rash or redness of the penis or foreskin (yeast infection)
- changes in urination (including urinating more frequently or in larger amounts, urgent need to urinate, need to urinate at night)
- constipation
- feeling thirsty
- feeling sick (nausea)
- blood tests may show changes in blood fat (cholesterol) levels and increases in the amount of red blood cells in your blood (haematocrit).

Uncommon (may affect up to 1 in 100 people)
- rash or red skin - this may be itchy and include raised bumps, oozing fluid or blisters
- hives
- blood tests may show changes related to kidney function (increased creatinine or urea) or increased potassium
- blood tests may show increases in your blood phosphate level
- bone fracture
- kidney failure (mainly as a consequence of loss of too much fluid from your body)
- lower limb amputations (mainly of the toe) especially if you are at high risk of heart disease
- phimosis – difficulty pulling back the foreskin around the tip of the penis.
- skin reactions after exposure to sunlight.

Not known (frequency cannot be estimated from the available data)
- necrotising fasciitis of the perineum or Fournier's gangrene, a serious soft tissue infection of the genitals or the area between the genitals and the anus.

Side effects when taking metformin alone that were not described for canagliflozin:
- very common: feeling sick (nausea), being sick (vomiting), diarrhoea, stomach ache, and loss of appetite
- common: a metallic taste (taste disturbance), decreased vitamin B_{12} levels (may cause anaemia – low count of red blood cells)
- very rare: liver function test disorders, hepatitis (a problem with your liver), and itching.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Vokanamet

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle and carton after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C.

Do not use Vokanamet if the packaging is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Vokanamet contains

- The active substances are canagliflozin and metformin hydrochloride.
  - Each 50 mg/850 mg tablet contains canagliflozin hemihydrate, equivalent to 50 mg of canagliflozin and 850 mg of metformin hydrochloride.
  - Each 50 mg/1,000 mg tablet contains canagliflozin hemihydrate, equivalent to 50 mg of canagliflozin and 1,000 mg of metformin hydrochloride.
  - Each 150 mg/850 mg tablet contains canagliflozin hemihydrate, equivalent to 150 mg of canagliflozin and 850 mg of metformin hydrochloride.
  - Each 150 mg/1,000 mg tablet contains canagliflozin hemihydrate, equivalent to 150 mg of canagliflozin and 1,000 mg of metformin hydrochloride.
- The other ingredients are:
  - Tablet core: microcrystalline cellulose, hypromellose, croscarmellose sodium, and magnesium stearate.
  - Film-coating:
    - 50 mg/850 mg tablets: macrogol 3350, poly(vinyl alcohol), talc, titanium dioxide (E171), iron oxide red (E172) and iron oxide black (E172).
    - 50 mg/1,000 mg tablets: macrogol 3350, poly(vinyl alcohol), talc, titanium dioxide (E171), iron oxide yellow (E172), and iron oxide red (E172).
    - 150 mg/850 mg tablets: macrogol 3350, poly(vinyl alcohol), talc, titanium dioxide (E171), and iron oxide yellow (E172).
    - 150 mg/1,000 mg tablets: macrogol 3350, poly(vinyl alcohol), talc, titanium dioxide (E171), iron oxide red (E172) and iron oxide black (E172).

What Vokanamet looks like and contents of the pack

- Vokanamet 50 mg/850 mg film-coated tablets (tablets) are pink, capsule-shaped, 20 mm in length, and debossed with “CM” on one side and “358” on the other side.
- Vokanamet 50 mg/1,000 mg film-coated tablets (tablets) are beige, capsule-shaped, 21 mm in length, and debossed with “CM” on one side and “551” on the other side.
- Vokanamet 150 mg/850 mg film-coated tablets (tablets) are light yellow, capsule-shaped, 21 mm in length, and debossed with “CM” on one side and “418” on the other side.
- Vokanamet 150 mg/1,000 mg film-coated tablets (tablets) are purple, capsule-shaped, 22 mm in length, and debossed with “CM” on one side and “611” on the other side.

Vokanamet is available in HDPE bottles with child-resistant closure. The pack sizes are cartons of 20 and 60 tablets, and multipack cartons of 180 tablets (3 bottles containing 60 tablets each).

Not all pack sizes may be marketed.

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.