

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Vokanamet 50 mg/850 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vokanamet is indicated in adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control:

- in patients not adequately controlled on their maximally tolerated doses of metformin alone
- in patients on their maximally tolerated doses of metformin along with other glucose-lowering medicinal products including insulin, when these do not provide adequate glycaemic control (see sections 4.4, 4.5, and 5.1 for available data on different add-on therapies)
- in patients already being treated with the combination of canagliflozin and metformin as separate tablets.

4.2 Posology and method of administration

Posology

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 (≥ 65 years old)

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).

Patients with renal impairment

For patients with an estimated glomerular filtration rate (eGFR) 60 mL/min/1.73 m² to < 90 mL/min/1.73m² or creatinine clearance (CrCl) of 60 mL/min to < 90 mL/min, no dose adjustment is needed.

Vokanamet must not be used in patients with moderate or severe renal impairment (eGFR < 60 mL/min/1.73m² or CrCl < 60 mL/min) due to the active substance metformin (see sections 4.3, 4.4 and 5.2).

Patients with hepatic impairment

Vokanamet is not recommended 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 impairment.

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 nearly time for the next dose in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time.

4.3 Contraindications

- Hypersensitivity to the active substances or any of the excipients (see section 6.1);
- Diabetic ketoacidosis, diabetic pre-coma;
- Moderate and severe renal impairment (patients with eGFR < 60 mL/min/1.73 m² or CrCl < 60 mL/min), (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

General

Vokanamet has not been studied in patients with type 1 diabetes and is therefore not recommended for use in these patients.

Lactic acidosis

Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic impairment, and any conditions associated with hypoxia.

Diagnosis

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.

This can be followed by acidotic dyspnea, abdominal pain, hypothermia and coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, treatment with the medicinal product should be discontinued and the patient should be hospitalised immediately (see section 4.9). Physicians should alert the patients on the risk and on the symptoms of lactic acidosis.

Renal function

As metformin is excreted by the kidney, and metformin accumulation may precipitate lactic acidosis, eGFR or creatinine clearance should be determined before initiating treatment and regularly thereafter:

- at least annually in patients with normal renal function
- at least two to four times a year in patients with eGFR (creatinine clearance) at the lower limit of normal and in elderly patients.

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 non-steroidal anti-inflammatory drug (NSAID).

Administration of iodinated contrast agent

The intravascular administration of iodinated contrast agents in radiologic studies can lead to renal failure. This may induce metformin accumulation which may increase the risk for lactic acidosis. Vokanamet must be discontinued prior to, or at the time of the test and not be reinstated until

48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see section 4.5).

Surgery

As Vokanamet contains metformin, therapy must be discontinued 48 hours before elective surgery with general, spinal, or peridural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and only if normal renal function has been established.

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 canagliflozin 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 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 cases, have been reported in clinical trials and post-marketing 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.

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 major surgical procedures or acute serious medical illnesses. In both cases, treatment with Vokanamet may be restarted once the patient's condition has stabilised.

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

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 trials suggest that DKA occurs with common frequency when patients with type 1 diabetes are treated with SGLT2 inhibitors.

Elevated haematocrit

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

Elderly (≥ 65 years old)

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 trials 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. In rare instances, phimosis was reported and sometimes circumcision was performed. 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.

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.

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 (2000 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 drug-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.

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.

Drug/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 glycemic control. Therefore, 1,5-AG assays should not be used for assessment of glycemic control in patients on Vokanamet. For further detail, it may be advisable to contact the specific manufacturer of the 1,5-AG assay.

METFORMIN

Combinations not recommended

Alcohol

There is an increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case 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 test and not reinstated until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see section 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

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 limited amount of data from the use of metformin in pregnant women does 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 safety profile

The safety of canagliflozin was evaluated in 10,285 patients with type 2 diabetes, including 5,151 patients treated with canagliflozin in combination with metformin. 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 $\geq 0.5\%$ 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 1) (see sections 4.2 and 4.4).

Tabulated list of adverse reactions

Adverse reactions in table 1 are based on the pooled analysis of the four 26-week placebo-controlled studies (n = 2,313) 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 (SOC). Frequency categories are defined according to the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Table 1: Tabulated list of adverse reactions (MedDRA) from placebo-controlled studies^a and from postmarketing experience

System organ class Frequency	Adverse reaction
<i>Metabolism and nutrition disorders</i>	
very common	Hypoglycaemia in combination with insulin or sulphonylurea
uncommon	Dehydration*
rare	Diabetic ketoacidosis**
<i>Nervous system disorders</i>	
uncommon	Dizziness postural*, Syncope*
<i>Vascular disorders</i>	
uncommon	Hypotension*, Orthostatic hypotension*
<i>Gastrointestinal disorders</i>	
common	Constipation, Thirst ^b , Nausea
<i>Skin and subcutaneous tissue disorders</i>	
uncommon	Rash ^c , Urticaria
not known	Angioedema ^d
<i>Musculoskeletal and connective tissue disorders</i>	
uncommon	Bone fracture ^e
<i>Renal and urinary disorders</i>	
common	Polyuria or Pollakiuria ^f , Urinary tract infection (pyelonephritis and urosepsis have been reported postmarketing)
uncommon	Renal failure (mainly in the context of volume depletion)
<i>Reproductive system and breast disorders</i>	
very common	Vulvovaginal candidiasis**·g
common	Balanitis or balanoposthitis**·h

Investigations	
common	Dyslipidemia ¹ , Haematocrit increased ^{**·j}
uncommon	Blood creatinine increased ^{**·k} , Blood urea increased ^{**·l} , Blood potassium increased ^{**·m} , Blood phosphate increased ⁿ

* Related to volume depletion; see section 4.4.

** See section 4.4.

^a 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-risk) were generally consistent with the adverse reactions identified in this table.

^b Thirst includes the terms thirst, dry mouth, and polydipsia.

^c Rash includes the terms rash erythematous, rash generalised, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, and rash vesicular.

^d Based on postmarketing experience with canagliflozin.

^e Bone fracture was reported in 0.7% and 0.6% for canagliflozin 100 mg and 300 mg, respectively, compared to 0.3% for placebo. See bone fracture section below for additional information.

^f Polyuria or pollakiuria includes the terms polyuria, pollakiuria, micturition urgency, nocturia, and urine output increased.

^g Vulvovaginal candidiasis includes the terms vulvovaginal candidiasis, vulvovaginal mycotic infection, vulvovaginitis, vaginal infection, vulvitis, and genital infection fungal.

^h Balanitis or balanoposthitis includes the terms balanitis, balanoposthitis, balanitis candida, and genital infection fungal.

ⁱ 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%.

^j 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.

^k 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.

^l 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.

^m 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.

ⁿ 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

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 the dedicated cardiovascular study, where patients were generally older with a higher rate of diabetes complications, the incidences of adverse reactions related to volume depletion were 2.8% with canagliflozin 100 mg once daily, 4.6% with canagliflozin 300 mg once daily, and 1.9% with placebo.

To assess risk factors for these adverse reactions, a larger pooled analysis (N = 9,439) of patients from eight controlled phase 3 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 m² to < 60 mL/min/1.73 m², and patients ≥ 75 years of age had generally higher incidences of these adverse reactions. For patients on loop diuretics, the incidences were 3.2% on canagliflozin 100 mg once daily and 8.8% on canagliflozin 300 mg once daily compared to 4.7% in the control group. For patients with a baseline eGFR 30 mL/min/1.73 m² to < 60 mL/min/1.73 m² or CrCl 30 to < 60 mL/min, the incidences were 4.8% on canagliflozin 100 mg once daily and 8.1% on canagliflozin 300 mg once daily compared to 2.6% in the control group. In patients ≥ 75 years of age, the incidences were 4.9%

on canagliflozin 100 mg once daily and 8.7% on canagliflozin 300 mg once daily compared to 2.6% in the control group (see sections 4.2 and 4.4).

In the dedicated cardiovascular study and the larger pooled analysis, 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).

Candidal balanitis or balanoposthitis was reported in 4.2% and 3.7% of male patients treated with canagliflozin 100 mg once daily and canagliflozin 300 mg once daily, respectively, compared to 0.6% in placebo-treated male patients. Among male patients taking canagliflozin, 0.9% had more than one infection. Overall, 0.5% of male patients discontinued canagliflozin due to candidal balanitis or balanoposthitis. In rare instances, phimosis was reported and sometimes circumcision was performed (see section 4.4).

Urinary tract infections

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. Subjects responded to standard treatments while continuing canagliflozin treatment.

Bone fracture

In a cardiovascular study of 4,327 patients with known or at high risk for cardiovascular disease, the incidence rates of bone fracture were 1.6, 1.6, and 1.1 per 100 patient years of exposure to canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively, with the fracture imbalance initially occurring within the first 26 weeks of therapy. In other type 2 diabetes studies with canagliflozin, which enrolled a general diabetes population of approximately 5,800 patients, no difference in fracture risk was observed relative to control. After 104 weeks of treatment, canagliflozin did not adversely affect bone mineral density.

Special populations

Elderly (≥ 65 years old)

In a pooled analysis of eight 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 incidences of 4.9%, 8.7% and 2.6% on canagliflozin 100 mg once daily, canagliflozin 300 mg once daily, and in the control group, respectively. Decreases in eGFR (-3.6% and -5.2%) were reported with canagliflozin 100 mg and canagliflozin 300 mg, respectively, compared to the control group (-3.0%) (see sections 4.2 and 4.4).

Metformin

Table 2 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 2: The frequency of metformin adverse reactions identified from clinical trial and postmarketing data

System organ class Frequency	Adverse reaction
<i>Metabolism and nutrition disorders</i>	
very rare	Lactic acidosis, Vitamin B ₁₂ deficiency ^a
<i>Nervous system disorders</i>	
common	Taste disturbance
<i>Gastrointestinal disorders</i>	
very common	Gastro-intestinal symptoms ^b
<i>Skin and subcutaneous tissue disorders</i>	
very rare	Erythema, Pruritis, Urticaria
<i>Hepatobiliary disorders</i>	
very rare	Liver function test abnormal, Hepatitis

^a Long-term treatment with metformin has been associated with a decrease in vitamin B₁₂ absorption, which may very rarely result in clinically significant vitamin B₁₂ deficiency (e.g., megaloblastic anaemia).

^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 1600 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 oral 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 antihyperglycemic 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%.

Clinical efficacy and safety

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

A total of 10,285 patients with type 2 diabetes participated in nine 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, 4% Black, and 8% other groups. 16% of patients were Hispanic. Approximately 58% of patients were male. Patients had an overall mean age of 59.6 years (range 21 years to 96 years), with 3,082 patients ≥ 65 years of age and 510 patients ≥ 75 years of age. 58% of patients had a body mass index (BMI) ≥ 30 kg/m².

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 3). 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.

Table 3: 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
	100 mg (N = 157)	300 mg (N = 156)	(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
	100 mg (N = 566)	300 mg (N = 587)	(N = 565)
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

^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).

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 4.

Table 4: 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 5). 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 5: 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 $p < 0.001$.

Special populations

In two studies conducted in special populations (older patients and patients with or at high risk for cardiovascular disease), canagliflozin was added to patients' current stable diabetes treatments (diet, monotherapy, or combination therapy).

Older patients

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).

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.

Cardiovascular safety

A pre-specified interim meta-analysis was conducted of adjudicated major cardiovascular events in the phase 2 and 3 clinical studies in 9,632 patients with type 2 diabetes, including 4,327 patients (44.9%) with cardiovascular disease or at high risk for cardiovascular disease who are participating in an ongoing cardiovascular study. The hazard ratio for the composite primary endpoint (time to event of cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, and unstable angina requiring hospitalisation) for canagliflozin (both doses pooled) *versus* combined active and placebo comparators was 0.91 (95% CI: 0.68; 1.22); therefore, there was no evidence of an increase in cardiovascular risk with canagliflozin relative to comparators. The hazard ratios for the canagliflozin 100 mg and 300 mg once daily doses were similar.

Blood pressure

In an analysis of four 26-week, placebo-controlled studies (N = 2,313), treatment with canagliflozin 100 mg and 300 mg once daily 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 once daily and 300 mg once daily 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 once daily, respectively.

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 diabetes-related 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/1000 mg, 150 mg/850 mg, and 150 mg/1000 mg combination tablets are bioequivalent to co-administration of corresponding doses of canagliflozin and metformin as individual tablets.

Administration of Vokanamet 150 mg/1000 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 intolerance 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 \pm 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 119 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 [¹⁴C]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

Patients with 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 Cockcroft-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 renal disease (ESRD) 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 ESRD subjects and healthy subjects.

Canagliflozin was negligibly removed by haemodialysis.

Patients with 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 (≥ 65 years old)

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

Studies characterising the pharmacokinetics of canagliflozin in paediatric patients have not been conducted.

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 trials, 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 Pre-clinical 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 \geq 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 1 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 0.6 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-fetal 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 300/2000 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

50 mg/850 mg:
Macrogol (3350)
Polyvinyl alcohol
Talc
Titanium dioxide (E171)
Iron oxide red (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 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
180 (3 x 60) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 April 2014

10. DATE OF REVISION OF THE TEXT

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

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Vokanamet 50 mg/1000 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains canagliflozin hemihydrate, equivalent to 50 mg of canagliflozin, and 1000 mg of metformin hydrochloride.

For the list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vokanamet is indicated in adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control:

- in patients not adequately controlled on their maximally tolerated doses of metformin alone
- in patients on their maximally tolerated doses of metformin along with other glucose-lowering medicinal products including insulin, when these do not provide adequate glycaemic control (see sections 4.4, 4.5, and 5.1 for available data on different add-on therapies)
- in patients already being treated with the combination of canagliflozin and metformin as separate tablets.

4.2 Posology and method of administration

Posology

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 (≥ 65 years old)

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).

Patients with renal impairment

For patients with an estimated glomerular filtration rate (eGFR) 60 mL/min/1.73 m² to < 90 mL/min/1.73m² or creatinine clearance (CrCl) of 60 mL/min to < 90 mL/min, no dose adjustment is needed.

Vokanamet must not be used in patients with moderate or severe renal impairment (eGFR < 60 mL/min/1.73m² or CrCl < 60 mL/min) due to the active substance metformin (see sections 4.3, 4.4 and 5.2).

Patients with hepatic impairment

Vokanamet is not recommended 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 impairment.

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 nearly time for the next dose in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time.

4.3 Contraindications

- Hypersensitivity to the active substances or any of the excipients (see section 6.1);
- Diabetic ketoacidosis, diabetic pre-coma;
- Moderate and severe renal impairment (patients with eGFR < 60 mL/min/1.73 m² or CrCl < 60 mL/min), (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

General

Vokanamet has not been studied in patients with type 1 diabetes and is therefore not recommended for use in these patients.

Lactic acidosis

Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic impairment, and any conditions associated with hypoxia.

Diagnosis

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.

This can be followed by acidotic dyspnea, abdominal pain, hypothermia and coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, treatment with the medicinal product should be discontinued and the patient should be hospitalised immediately (see section 4.9). Physicians should alert the patients on the risk and on the symptoms of lactic acidosis.

Renal function

As metformin is excreted by the kidney, and metformin accumulation may precipitate lactic acidosis, eGFR or creatinine clearance should be determined before initiating treatment and regularly thereafter:

- at least annually in patients with normal renal function
- at least two to four times a year in patients with eGFR (creatinine clearance) at the lower limit of normal and in elderly patients.

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 non-steroidal anti-inflammatory drug (NSAID).

Administration of iodinated contrast agent

The intravascular administration of iodinated contrast agents in radiologic studies can lead to renal failure. This may induce metformin accumulation which may increase the risk for lactic acidosis. Vokanamet must be discontinued prior to, or at the time of the test and not be reinstated until

48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see section 4.5).

Surgery

As Vokanamet contains metformin, therapy must be discontinued 48 hours before elective surgery with general, spinal, or peridural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and only if normal renal function has been established.

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 canagliflozin 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 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 cases, have been reported in clinical trials and post-marketing 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.

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 major surgical procedures or acute serious medical illnesses. In both cases, treatment with Vokanamet may be restarted once the patient's condition has stabilised.

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

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 trials suggest that DKA occurs with common frequency when patients with type 1 diabetes are treated with SGLT2 inhibitors.

Elevated haematocrit

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

Elderly (≥ 65 years old)

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 trials 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. In rare instances, phimosis was reported and sometimes circumcision was performed. 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.

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.

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 (2000 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 drug-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.

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.

Drug/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 glycemic control. Therefore, 1,5-AG assays should not be used for assessment of glycemic control in patients on Vokanamet. For further detail, it may be advisable to contact the specific manufacturer of the 1,5-AG assay.

METFORMIN

Combinations not recommended

Alcohol

There is an increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case 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 test and not reinstated until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see section 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

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 limited amount of data from the use of metformin in pregnant women does 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 safety profile

The safety of canagliflozin was evaluated in 10,285 patients with type 2 diabetes, including 5,151 patients treated with canagliflozin in combination with metformin. 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 $\geq 0.5\%$ 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 1) (see sections 4.2 and 4.4).

Tabulated list of adverse reactions

Adverse reactions in table 1 are based on the pooled analysis of the four 26-week placebo-controlled studies (n=2,313) 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 (SOC). Frequency categories are defined according to the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Table 1: Tabulated list of adverse reactions (MedDRA) from placebo-controlled studies^a and from postmarketing experience

System organ class Frequency	Adverse reaction
<i>Metabolism and nutrition disorders</i>	
very common	Hypoglycaemia in combination with insulin or sulphonylurea
uncommon	Dehydration*
rare	Diabetic ketoacidosis**
<i>Nervous system disorders</i>	
uncommon	Dizziness postural*, Syncope*
<i>Vascular disorders</i>	
uncommon	Hypotension*, Orthostatic hypotension*
<i>Gastrointestinal disorders</i>	
common	Constipation, Thirst ^b , Nausea
<i>Skin and subcutaneous tissue disorders</i>	
uncommon	Rash ^c , Urticaria
not known	Angioedema ^d
<i>Musculoskeletal and connective tissue disorders</i>	
uncommon	Bone fracture ^e
<i>Renal and urinary disorders</i>	
common	Polyuria or Pollakiuria ^f , Urinary tract infection (pyelonephritis and urosepsis have been reported postmarketing)
uncommon	Renal failure (mainly in the context of volume depletion)
<i>Reproductive system and breast disorders</i>	
very common	Vulvovaginal candidiasis***, ^g
common	Balanitis or balanoposthitis***, ^h
<i>Investigations</i>	
common	Dyslipidemia ⁱ , Haematocrit increased***, ^j

uncommon	Blood creatinine increased ^{**·k} , Blood urea increased ^{**·l} , Blood potassium increased ^{**·m} , Blood phosphate increased ⁿ
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* Related to volume depletion; see section 4.4.

** See section 4.4.

^a 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-risk) were generally consistent with the adverse reactions identified in this table.

^b Thirst includes the terms thirst, dry mouth, and polydipsia.

^c Rash includes the terms rash erythematous, rash generalised, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, and rash vesicular.

^d Based on postmarketing experience with canagliflozin.

^e Bone fracture was reported in 0.7% and 0.6% for canagliflozin 100 mg and 300 mg, respectively, compared to 0.3% for placebo. See bone fracture section below for additional information.

^f Polyuria or pollakiuria includes the terms polyuria, pollakiuria, micturition urgency, nocturia, and urine output increased.

^g Vulvovaginal candidiasis includes the terms vulvovaginal candidiasis, vulvovaginal mycotic infection, vulvovaginitis, vaginal infection, vulvitis, and genital infection fungal.

^h Balanitis or balanoposthitis includes the terms balanitis, balanoposthitis, balanitis candida, and genital infection fungal.

ⁱ 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%.

^j 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.

^k 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.

^l 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.

^m 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.

ⁿ 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

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 the dedicated cardiovascular study, where patients were generally older with a higher rate of diabetes complications, the incidences of adverse reactions related to volume depletion were 2.8% with canagliflozin 100 mg once daily, 4.6% with canagliflozin 300 mg once daily, and 1.9% with placebo.

To assess risk factors for these adverse reactions, a larger pooled analysis (N=9,439) of patients from eight controlled phase 3 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 m² to < 60 mL/min/1.73 m², and patients ≥ 75 years of age had generally higher incidences of these adverse reactions. For patients on loop diuretics, the incidences were 3.2% on canagliflozin 100 mg once daily and 8.8% on canagliflozin 300 mg once daily compared to 4.7% in the control group. For patients with a baseline eGFR 30 mL/min/1.73 m² to < 60 mL/min/1.73 m² or CrCl 30 to < 60 mL/min, the incidences were 4.8% on canagliflozin 100 mg once daily and 8.1% on canagliflozin 300 mg once daily compared to 2.6% in the control group. In patients ≥ 75 years of age, the incidences were 4.9% on canagliflozin 100 mg once daily and 8.7% on canagliflozin 300 mg once daily compared to 2.6% in the control group (see sections 4.2 and 4.4).

In the dedicated cardiovascular study and the larger pooled analysis, 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).

Candidal balanitis or balanoposthitis was reported in 4.2% and 3.7% of male patients treated with canagliflozin 100 mg once daily and canagliflozin 300 mg once daily, respectively, compared to 0.6% in placebo-treated male patients. Among male patients taking canagliflozin, 0.9% had more than one infection. Overall, 0.5% of male patients discontinued canagliflozin due to candidal balanitis or balanoposthitis. In rare instances, phimosis was reported and sometimes circumcision was performed (see section 4.4).

Urinary tract infections

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. Subjects responded to standard treatments while continuing canagliflozin treatment.

Bone fracture

In a cardiovascular study of 4,327 patients with known or at high risk for cardiovascular disease, the incidence rates of bone fracture were 1.6, 1.6, and 1.1 per 100 patient years of exposure to canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively, with the fracture imbalance initially occurring within the first 26 weeks of therapy. In other type 2 diabetes studies with canagliflozin, which enrolled a general diabetes population of approximately 5,800 patients, no difference in fracture risk was observed relative to control. After 104 weeks of treatment, canagliflozin did not adversely affect bone mineral density.

Special populations

Elderly (≥ 65 years old)

In a pooled analysis of eight 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 incidences of 4.9%, 8.7% and 2.6% on canagliflozin 100 mg once daily, canagliflozin 300 mg once daily, and in the control group, respectively. Decreases in eGFR (-3.6% and -5.2%) were reported with canagliflozin 100 mg and canagliflozin 300 mg, respectively, compared to the control group (-3.0%) (see sections 4.2 and 4.4).

Metformin

Table 2 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 2: The frequency of metformin adverse reactions identified from clinical trial and postmarketing data

System organ class Frequency	Adverse reaction
<i>Metabolism and nutrition disorders</i>	
very rare	Lactic acidosis, Vitamin B ₁₂ deficiency ^a
<i>Nervous system disorders</i>	
common	Taste disturbance
<i>Gastrointestinal disorders</i>	
very common	Gastro-intestinal symptoms ^b
<i>Skin and subcutaneous tissue disorders</i>	
very rare	Erythema, Pruritis, Urticaria
<i>Hepatobiliary disorders</i>	
very rare	Liver function test abnormal, Hepatitis

^a Long-term treatment with metformin has been associated with a decrease in vitamin B₁₂ absorption, which may very rarely result in clinically significant vitamin B₁₂ deficiency (e.g., megaloblastic anaemia).

^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 1600 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 oral 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 antihyperglycemic 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%.

Clinical efficacy and safety

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

A total of 10,285 patients with type 2 diabetes participated in nine 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, 4% Black, and 8% other groups. 16% of patients were Hispanic. Approximately 58% of patients were male. Patients had an overall mean age of 59.6 years (range 21 years to 96 years), with 3,082 patients ≥ 65 years of age and 510 patients ≥ 75 years of age. 58% of patients had a body mass index (BMI) ≥ 30 kg/m².

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 3). 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.

Table 3: Efficacy results from placebo-controlled clinical studies^a

Dual therapy with metformin (26 weeks)			
	Canagliflozin + metformin		Placebo + metformin
	100 mg (N=368)	300 mg (N=367)	(N=183)
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

^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).

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 glycemic 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 4.

Table 4: 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 5). 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 5: 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
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^a Intent-to-treat population using last observation in study prior to glycaemic rescue therapy.

^b $p < 0.05$.

^c Not applicable.

^d $p < 0.001$.

Special populations

In two studies conducted in special populations (older patients and patients with or at high risk for cardiovascular disease), canagliflozin was added to patients' current stable diabetes treatments (diet, monotherapy, or combination therapy).

Older patients

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).

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.

Cardiovascular safety

A pre-specified interim meta-analysis was conducted of adjudicated major cardiovascular events in the phase 2 and 3 clinical studies in 9,632 patients with type 2 diabetes, including 4,327 patients (44.9%) with cardiovascular disease or at high risk for cardiovascular disease who are participating in an

ongoing cardiovascular study. The hazard ratio for the composite primary endpoint (time to event of cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, and unstable angina requiring hospitalisation) for canagliflozin (both doses pooled) *versus* combined active and placebo comparators was 0.91 (95% CI: 0.68; 1.22); therefore, there was no evidence of an increase in cardiovascular risk with canagliflozin relative to comparators. The hazard ratios for the canagliflozin 100 mg and 300 mg once daily doses were similar.

Blood pressure

In an analysis of four 26-week, placebo-controlled studies (N=2,313), treatment with canagliflozin 100 mg and 300 mg once daily 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 once daily and 300 mg once daily 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 once daily, respectively.

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 diabetes-related 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/1000 mg, 150 mg/850 mg, and 150 mg/1000 mg combination tablets are bioequivalent to co-administration of corresponding doses of canagliflozin and metformin as individual tablets.

Administration of Vokanamet 150 mg/1000 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 intolerance 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 \pm 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 119 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

Patients with 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 Cockcroft-Gault equation) compared to healthy subjects. The study included 8 subjects with normal renal function (CrCl \geq 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 renal disease (ESRD) 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 ESRD subjects and healthy subjects.

Canagliflozin was negligibly removed by haemodialysis.

Patients with 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 (\geq 65 years old)

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

Studies characterising the pharmacokinetics of canagliflozin in paediatric patients have not been conducted.

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 trials, 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 Pre-clinical 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 \geq 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 1 through day 90 postnatal did not show increased sensitivity compared to effects observed in adult rats. However, dilatation of the renal pelvis was noticed with a No Observed Effect Level (NOEL) at exposures 2.4 times and 0.6 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-fetal 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 300/2000 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

50 mg/1000 mg:
Macrogol (3350)
Polyvinyl alcohol
Talc
Titanium dioxide (E171))
Iron oxide yellow (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 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
180 (3 x 60) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 April 2014

10. DATE OF REVISION OF THE TEXT

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

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Vokanamet 150 mg/850 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vokanamet is indicated in adults aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control:

- in patients not adequately controlled on their maximally tolerated doses of metformin alone
- in patients on their maximally tolerated doses of metformin along with other glucose-lowering medicinal products including insulin, when these do not provide adequate glycaemic control (see sections 4.4, 4.5, and 5.1 for available data on different add-on therapies)
- in patients already being treated with the combination of canagliflozin and metformin as separate tablets.

4.2 Posology and method of administration

Posology

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 (≥ 65 years old)

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).

Patients with renal impairment

For patients with an estimated glomerular filtration rate (eGFR) 60 mL/min/1.73 m² to < 90 mL/min/1.73m² or creatinine clearance (CrCl) of 60 mL/min to < 90 mL/min, no dose adjustment is needed.

Vokanamet must not be used in patients with moderate or severe renal impairment (eGFR < 60 mL/min/1.73m² or CrCl < 60 mL/min) due to the active substance metformin (see sections 4.3, 4.4 and 5.2).

Patients with hepatic impairment

Vokanamet is not recommended 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 impairment.

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 nearly time for the next dose in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time.

4.3 Contraindications

- Hypersensitivity to the active substances or any of the excipients (see section 6.1);
- Diabetic ketoacidosis, diabetic pre-coma;
- Moderate and severe renal impairment (patients with eGFR < 60 mL/min/1.73 m² or CrCl < 60 mL/min), (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

General

Vokanamet has not been studied in patients with type 1 diabetes and is therefore not recommended for use in these patients.

Lactic acidosis

Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic impairment, and any conditions associated with hypoxia.

Diagnosis

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.

This can be followed by acidotic dyspnea, abdominal pain, hypothermia and coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, treatment with the medicinal product should be discontinued and the patient should be hospitalised immediately (see section 4.9). Physicians should alert the patients on the risk and on the symptoms of lactic acidosis.

Renal function

As metformin is excreted by the kidney, and metformin accumulation may precipitate lactic acidosis, eGFR or creatinine clearance should be determined before initiating treatment and regularly thereafter:

- at least annually in patients with normal renal function
- at least two to four times a year in patients with eGFR (creatinine clearance) at the lower limit of normal and in elderly patients.

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 non-steroidal anti-inflammatory drug (NSAID).

Administration of iodinated contrast agent

The intravascular administration of iodinated contrast agents in radiologic studies can lead to renal failure. This may induce metformin accumulation which may increase the risk for lactic acidosis. Vokanamet must be discontinued prior to, or at the time of the test and not be reinstated until

48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see section 4.5).

Surgery

As Vokanamet contains metformin, therapy must be discontinued 48 hours before elective surgery with general, spinal, or peridural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and only if normal renal function has been established.

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 canagliflozin 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 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 cases, have been reported in clinical trials and post-marketing 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.

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 major surgical procedures or acute serious medical illnesses. In both cases, treatment with Vokanamet may be restarted once the patient's condition has stabilised.

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

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 trials suggest that DKA occurs with common frequency when patients with type 1 diabetes are treated with SGLT2 inhibitors.

Elevated haematocrit

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

Elderly (≥ 65 years old)

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 trials 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. In rare instances, phimosis was reported and sometimes circumcision was performed. 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.

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.

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 (2000 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 drug-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.

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.

Drug/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 glycemic control. Therefore, 1,5-AG assays should not be used for assessment of glycemic control in patients on Vokanamet. For further detail, it may be advisable to contact the specific manufacturer of the 1,5-AG assay.

METFORMIN

Combinations not recommended

Alcohol

There is an increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case 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 test and not reinstated until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see section 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

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 limited amount of data from the use of metformin in pregnant women does 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 safety profile

The safety of canagliflozin was evaluated in 10,285 patients with type 2 diabetes, including 5,151 patients treated with canagliflozin in combination with metformin. 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 $\geq 0.5\%$ 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 1) (see sections 4.2 and 4.4).

Tabulated list of adverse reactions

Adverse reactions in table 1 are based on the pooled analysis of the four 26-week placebo-controlled studies (n=2,313) 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 (SOC). Frequency categories are defined according to the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Table 1: Tabulated list of adverse reactions (MedDRA) from placebo-controlled studies^a and from postmarketing experience

System organ class Frequency	Adverse reaction
<i>Metabolism and nutrition disorders</i>	
very common	Hypoglycaemia in combination with insulin or sulphonylurea
uncommon	Dehydration*
rare	Diabetic ketoacidosis**
<i>Nervous system disorders</i>	
uncommon	Dizziness postural*, Syncope*
<i>Vascular disorders</i>	
uncommon	Hypotension*, Orthostatic hypotension*
<i>Gastrointestinal disorders</i>	
common	Constipation, Thirst ^b , Nausea
<i>Skin and subcutaneous tissue disorders</i>	
uncommon	Rash ^c , Urticaria
not known	Angioedema ^d
<i>Musculoskeletal and connective tissue disorders</i>	
uncommon	Bone fracture ^e
<i>Renal and urinary disorders</i>	
common	Polyuria or Pollakiuria ^f , Urinary tract infection (pyelonephritis and urosepsis have been reported postmarketing)
uncommon	Renal failure (mainly in the context of volume depletion)
<i>Reproductive system and breast disorders</i>	
very common	Vulvovaginal candidiasis***, ^g
common	Balanitis or balanoposthitis***, ^h
<i>Investigations</i>	
common	Dyslipidemia ⁱ , Haematocrit increased***, ^j

uncommon	Blood creatinine increased ^{**·k} , Blood urea increased ^{**·l} , Blood potassium increased ^{**·m} , Blood phosphate increased ⁿ
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* Related to volume depletion; see section 4.4.

** See section 4.4.

^a 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-risk) were generally consistent with the adverse reactions identified in this table.

^b Thirst includes the terms thirst, dry mouth, and polydipsia.

^c Rash includes the terms rash erythematous, rash generalised, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, and rash vesicular.

^d Based on postmarketing experience with canagliflozin.

^e Bone fracture was reported in 0.7% and 0.6% for canagliflozin 100 mg and 300 mg, respectively, compared to 0.3% for placebo. See bone fracture section below for additional information.

^f Polyuria or pollakiuria includes the terms polyuria, pollakiuria, micturition urgency, nocturia, and urine output increased.

^g Vulvovaginal candidiasis includes the terms vulvovaginal candidiasis, vulvovaginal mycotic infection, vulvovaginitis, vaginal infection, vulvitis, and genital infection fungal.

^h Balanitis or balanoposthitis includes the terms balanitis, balanoposthitis, balanitis candida, and genital infection fungal.

ⁱ 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%.

^j 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.

^k 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.

^l 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.

^m 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.

ⁿ 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

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 the dedicated cardiovascular study, where patients were generally older with a higher rate of diabetes complications, the incidences of adverse reactions related to volume depletion were 2.8% with canagliflozin 100 mg once daily, 4.6% with canagliflozin 300 mg once daily, and 1.9% with placebo.

To assess risk factors for these adverse reactions, a larger pooled analysis (N=9,439) of patients from eight controlled phase 3 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 m² to < 60 mL/min/1.73 m², and patients ≥ 75 years of age had generally higher incidences of these adverse reactions. For patients on loop diuretics, the incidences were 3.2% on canagliflozin 100 mg once daily and 8.8% on canagliflozin 300 mg once daily compared to 4.7% in the control group. For patients with a baseline eGFR 30 mL/min/1.73 m² to < 60 mL/min/1.73 m² or CrCl 30 to < 60 mL/min, the incidences were 4.8% on canagliflozin 100 mg once daily and 8.1% on canagliflozin 300 mg once daily compared to 2.6% in the control group. In patients ≥ 75 years of age, the incidences were 4.9% on canagliflozin 100 mg once daily and 8.7% on canagliflozin 300 mg once daily compared to 2.6% in the control group (see sections 4.2 and 4.4).

In the dedicated cardiovascular study and the larger pooled analysis, 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).

Candidal balanitis or balanoposthitis was reported in 4.2% and 3.7% of male patients treated with canagliflozin 100 mg once daily and canagliflozin 300 mg once daily, respectively, compared to 0.6% in placebo-treated male patients. Among male patients taking canagliflozin, 0.9% had more than one infection. Overall, 0.5% of male patients discontinued canagliflozin due to candidal balanitis or balanoposthitis. In rare instances, phimosis was reported and sometimes circumcision was performed (see section 4.4).

Urinary tract infections

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. Subjects responded to standard treatments while continuing canagliflozin treatment.

Bone fracture

In a cardiovascular study of 4,327 patients with known or at high risk for cardiovascular disease, the incidence rates of bone fracture were 1.6, 1.6, and 1.1 per 100 patient years of exposure to canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively, with the fracture imbalance initially occurring within the first 26 weeks of therapy. In other type 2 diabetes studies with canagliflozin, which enrolled a general diabetes population of approximately 5,800 patients, no difference in fracture risk was observed relative to control. After 104 weeks of treatment, canagliflozin did not adversely affect bone mineral density.

Special populations

Elderly (≥ 65 years old)

In a pooled analysis of eight 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 incidences of 4.9%, 8.7% and 2.6% on canagliflozin 100 mg once daily, canagliflozin 300 mg once daily, and in the control group, respectively. Decreases in eGFR (-3.6% and -5.2%) were reported with canagliflozin 100 mg and canagliflozin 300 mg, respectively, compared to the control group (-3.0%) (see sections 4.2 and 4.4).

Metformin

Table 2 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 2: The frequency of metformin adverse reactions identified from clinical trial and postmarketing data

System organ class Frequency	Adverse reaction
<i>Metabolism and nutrition disorders</i>	
very rare	Lactic acidosis, Vitamin B ₁₂ deficiency ^a
<i>Nervous system disorders</i>	
common	Taste disturbance
<i>Gastrointestinal disorders</i>	
very common	Gastro-intestinal symptoms ^b
<i>Skin and subcutaneous tissue disorders</i>	
very rare	Erythema, Pruritis, Urticaria
<i>Hepatobiliary disorders</i>	
very rare	Liver function test abnormal, Hepatitis

^a Long-term treatment with metformin has been associated with a decrease in vitamin B₁₂ absorption, which may very rarely result in clinically significant vitamin B₁₂ deficiency (e.g., megaloblastic anaemia).

^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 1600 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 oral 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 antihyperglycemic 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%.

Clinical efficacy and safety

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

A total of 10,285 patients with type 2 diabetes participated in nine 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, 4% Black, and 8% other groups. 16% of patients were Hispanic. Approximately 58% of patients were male. Patients had an overall mean age of 59.6 years (range 21 years to 96 years), with 3,082 patients ≥ 65 years of age and 510 patients ≥ 75 years of age. 58% of patients had a body mass index (BMI) ≥ 30 kg/m².

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 3). 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.

Table 3: Efficacy results from placebo-controlled clinical studies^a

Dual therapy with metformin (26 weeks)			
	Canagliflozin + metformin		Placebo + metformin
	100 mg (N=368)	300 mg (N=367)	(N=183)
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

^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).

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 glycemic 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 4.

Table 4: 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 5). 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 5: 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
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^a Intent-to-treat population using last observation in study prior to glycaemic rescue therapy.

^b $p < 0.05$.

^c Not applicable.

^d $p < 0.001$.

Special populations

In two studies conducted in special populations (older patients and patients with or at high risk for cardiovascular disease), canagliflozin was added to patients' current stable diabetes treatments (diet, monotherapy, or combination therapy).

Older patients

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).

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.

Cardiovascular safety

A pre-specified interim meta-analysis was conducted of adjudicated major cardiovascular events in the phase 2 and 3 clinical studies in 9,632 patients with type 2 diabetes, including 4,327 patients (44.9%) with cardiovascular disease or at high risk for cardiovascular disease who are participating in an

ongoing cardiovascular study. The hazard ratio for the composite primary endpoint (time to event of cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, and unstable angina requiring hospitalisation) for canagliflozin (both doses pooled) *versus* combined active and placebo comparators was 0.91 (95% CI: 0.68; 1.22); therefore, there was no evidence of an increase in cardiovascular risk with canagliflozin relative to comparators. The hazard ratios for the canagliflozin 100 mg and 300 mg once daily doses were similar.

Blood pressure

In an analysis of four 26-week, placebo-controlled studies (N=2,313), treatment with canagliflozin 100 mg and 300 mg once daily 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 once daily and 300 mg once daily 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 once daily, respectively.

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 diabetes-related 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/1000 mg, 150 mg/850 mg, and 150 mg/1000 mg combination tablets are bioequivalent to co-administration of corresponding doses of canagliflozin and metformin as individual tablets.

Administration of Vokanamet 150 mg/1000 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 intolerance 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 \pm 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 119 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

Patients with 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 Cockcroft-Gault equation) compared to healthy subjects. The study included 8 subjects with normal renal function (CrCl \geq 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 renal disease (ESRD) 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 ESRD subjects and healthy subjects.

Canagliflozin was negligibly removed by haemodialysis.

Patients with 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 (\geq 65 years old)

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

Studies characterising the pharmacokinetics of canagliflozin in paediatric patients have not been conducted.

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 trials, 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 Pre-clinical 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 \geq 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 1 through day 90 postnatal did not show increased sensitivity compared to effects observed in adult rats. However, dilatation of the renal pelvis was noticed with a No Observed Effect Level (NOEL) at exposures 2.4 times and 0.6 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-fetal 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 300/2000 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

150 mg/850 mg:
Macrogol (3350)
Polyvinyl alcohol
Talc
Titanium dioxide (E171)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 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
180 (3 x 60) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 April 2014

10. DATE OF REVISION OF THE TEXT

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

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Vokanamet 150 mg/1000 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains canagliflozin hemihydrate, equivalent to 150 mg of canagliflozin, and 1000 mg of metformin hydrochloride.

For the list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

The tablet is purple, capsule-shaped, 22 mm in length, immediate-release, 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 aged 18 years and older with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control:

- in patients not adequately controlled on their maximally tolerated doses of metformin alone
- in patients on their maximally tolerated doses of metformin along with other glucose-lowering medicinal products including insulin, when these do not provide adequate glycaemic control (see sections 4.4, 4.5, and 5.1 for available data on different add-on therapies)
- in patients already being treated with the combination of canagliflozin and metformin as separate tablets.

4.2 Posology and method of administration

Posology

The dose of glucose-lowering therapy with Vokanamet should be individualised on the basis of the patient’s current regimen, effectiveness, and tolerability, while 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 (≥ 65 years old)

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).

Patients with renal impairment

For patients with an estimated glomerular filtration rate (eGFR) 60 mL/min/1.73 m² to < 90 mL/min/1.73m² or creatinine clearance (CrCl) of 60 mL/min to < 90 mL/min, no dose adjustment is needed.

Vokanamet must not be used in patients with moderate or severe renal impairment (eGFR < 60 mL/min/1.73m² or CrCl < 60 mL/min) due to the active substance metformin (see sections 4.3, 4.4 and 5.2).

Patients with hepatic impairment

Vokanamet is not recommended 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 impairment.

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 nearly time for the next dose in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time.

4.3 Contraindications

- Hypersensitivity to the active substances or any of the excipients (see section 6.1);
- Diabetic ketoacidosis, diabetic pre-coma;
- Moderate and severe renal impairment (patients with eGFR < 60 mL/min/1.73 m² or CrCl < 60 mL/min), (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

General

Vokanamet has not been studied in patients with type 1 diabetes and is therefore not recommended for use in these patients.

Lactic acidosis

Lactic acidosis is a rare, but serious (high mortality in the absence of prompt treatment), metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic impairment, and any conditions associated with hypoxia.

Diagnosis

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.

This can be followed by acidotic dyspnea, abdominal pain, hypothermia and coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, treatment with the medicinal product should be discontinued and the patient should be hospitalised immediately (see section 4.9). Physicians should alert the patients on the risk and on the symptoms of lactic acidosis.

Renal function

As metformin is excreted by the kidney, and metformin accumulation may precipitate lactic acidosis, eGFR or creatinine clearance should be determined before initiating treatment and regularly thereafter:

- at least annually in patients with normal renal function
- at least two to four times a year in patients with eGFR (creatinine clearance) at the lower limit of normal and in elderly patients.

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 non-steroidal anti-inflammatory drug (NSAID).

Administration of iodinated contrast agent

The intravascular administration of iodinated contrast agents in radiologic studies can lead to renal failure. This may induce metformin accumulation which may increase the risk for lactic acidosis. Vokanamet must be discontinued prior to, or at the time of the test and not be reinstated until

48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see section 4.5).

Surgery

As Vokanamet contains metformin, therapy must be discontinued 48 hours before elective surgery with general, spinal, or peridural anaesthesia. Therapy may be restarted no earlier than 48 hours following surgery or resumption of oral nutrition and only if normal renal function has been established.

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 canagliflozin 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 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 cases, have been reported in clinical trials and post-marketing 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.

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 major surgical procedures or acute serious medical illnesses. In both cases, treatment with Vokanamet may be restarted once the patient's condition has stabilised.

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

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 trials suggest that DKA occurs with common frequency when patients with type 1 diabetes are treated with SGLT2 inhibitors.

Elevated haematocrit

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

Elderly (≥ 65 years old)

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 trials 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. In rare instances, phimosis was reported and sometimes circumcision was performed. 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.

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.

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 (2000 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 drug-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.

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.

Drug/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 glycemic control. Therefore, 1,5-AG assays should not be used for assessment of glycemic control in patients on Vokanamet. For further detail, it may be advisable to contact the specific manufacturer of the 1,5-AG assay.

METFORMIN

Combinations not recommended

Alcohol

There is an increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case 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 test and not reinstated until 48 hours afterwards, and only after renal function has been re-evaluated and found to be normal (see section 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

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 limited amount of data from the use of metformin in pregnant women does 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 safety profile

The safety of canagliflozin was evaluated in 10,285 patients with type 2 diabetes, including 5,151 patients treated with canagliflozin in combination with metformin. 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 $\geq 0.5\%$ 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 1) (see sections 4.2 and 4.4).

Tabulated list of adverse reactions

Adverse reactions in table 1 are based on the pooled analysis of the four 26-week placebo-controlled studies (n=2,313) 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 (SOC). Frequency categories are defined according to the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Table 1: Tabulated list of adverse reactions (MedDRA) from placebo-controlled studies^a and from postmarketing experience

System organ class Frequency	Adverse reaction
<i>Metabolism and nutrition disorders</i>	
very common	Hypoglycaemia in combination with insulin or sulphonylurea
uncommon	Dehydration*
rare	Diabetic ketoacidosis**
<i>Nervous system disorders</i>	
uncommon	Dizziness postural*, Syncope*
<i>Vascular disorders</i>	
uncommon	Hypotension*, Orthostatic hypotension*
<i>Gastrointestinal disorders</i>	
common	Constipation, Thirst ^b , Nausea
<i>Skin and subcutaneous tissue disorders</i>	
uncommon	Rash ^c , Urticaria
not known	Angioedema ^d
<i>Musculoskeletal and connective tissue disorders</i>	
uncommon	Bone fracture ^e
<i>Renal and urinary disorders</i>	
common	Polyuria or Pollakiuria ^f , Urinary tract infection (pyelonephritis and urosepsis have been reported postmarketing)
uncommon	Renal failure (mainly in the context of volume depletion)
<i>Reproductive system and breast disorders</i>	
very common	Vulvovaginal candidiasis***, ^g
common	Balanitis or balanoposthitis***, ^h
<i>Investigations</i>	
common	Dyslipidemia ⁱ , Haematocrit increased***, ^j

uncommon	Blood creatinine increased ^{**·k} , Blood urea increased ^{**·l} , Blood potassium increased ^{**·m} , Blood phosphate increased ⁿ
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* Related to volume depletion; see section 4.4.

** See section 4.4.

^a 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-risk) were generally consistent with the adverse reactions identified in this table.

^b Thirst includes the terms thirst, dry mouth, and polydipsia.

^c Rash includes the terms rash erythematous, rash generalised, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, and rash vesicular.

^d Based on postmarketing experience with canagliflozin.

^e Bone fracture was reported in 0.7% and 0.6% for canagliflozin 100 mg and 300 mg, respectively, compared to 0.3% for placebo. See bone fracture section below for additional information.

^f Polyuria or pollakiuria includes the terms polyuria, pollakiuria, micturition urgency, nocturia, and urine output increased.

^g Vulvovaginal candidiasis includes the terms vulvovaginal candidiasis, vulvovaginal mycotic infection, vulvovaginitis, vaginal infection, vulvitis, and genital infection fungal.

^h Balanitis or balanoposthitis includes the terms balanitis, balanoposthitis, balanitis candida, and genital infection fungal.

ⁱ 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%.

^j 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.

^k 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.

^l 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.

^m 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.

ⁿ 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

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 the dedicated cardiovascular study, where patients were generally older with a higher rate of diabetes complications, the incidences of adverse reactions related to volume depletion were 2.8% with canagliflozin 100 mg once daily, 4.6% with canagliflozin 300 mg once daily, and 1.9% with placebo.

To assess risk factors for these adverse reactions, a larger pooled analysis (N=9,439) of patients from eight controlled phase 3 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 m² to < 60 mL/min/1.73 m², and patients ≥ 75 years of age had generally higher incidences of these adverse reactions. For patients on loop diuretics, the incidences were 3.2% on canagliflozin 100 mg once daily and 8.8% on canagliflozin 300 mg once daily compared to 4.7% in the control group. For patients with a baseline eGFR 30 mL/min/1.73 m² to < 60 mL/min/1.73 m² or CrCl 30 to < 60 mL/min, the incidences were 4.8% on canagliflozin 100 mg once daily and 8.1% on canagliflozin 300 mg once daily compared to 2.6% in the control group. In patients ≥ 75 years of age, the incidences were 4.9% on canagliflozin 100 mg once daily and 8.7% on canagliflozin 300 mg once daily compared to 2.6% in the control group (see sections 4.2 and 4.4).

In the dedicated cardiovascular study and the larger pooled analysis, 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).

Candidal balanitis or balanoposthitis was reported in 4.2% and 3.7% of male patients treated with canagliflozin 100 mg once daily and canagliflozin 300 mg once daily, respectively, compared to 0.6% in placebo-treated male patients. Among male patients taking canagliflozin, 0.9% had more than one infection. Overall, 0.5% of male patients discontinued canagliflozin due to candidal balanitis or balanoposthitis. In rare instances, phimosis was reported and sometimes circumcision was performed (see section 4.4).

Urinary tract infections

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. Subjects responded to standard treatments while continuing canagliflozin treatment.

Bone fracture

In a cardiovascular study of 4,327 patients with known or at high risk for cardiovascular disease, the incidence rates of bone fracture were 1.6, 1.6, and 1.1 per 100 patient years of exposure to canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively, with the fracture imbalance initially occurring within the first 26 weeks of therapy. In other type 2 diabetes studies with canagliflozin, which enrolled a general diabetes population of approximately 5,800 patients, no difference in fracture risk was observed relative to control. After 104 weeks of treatment, canagliflozin did not adversely affect bone mineral density.

Special populations

Elderly (≥ 65 years old)

In a pooled analysis of eight 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 incidences of 4.9%, 8.7% and 2.6% on canagliflozin 100 mg once daily, canagliflozin 300 mg once daily, and in the control group, respectively. Decreases in eGFR (-3.6% and -5.2%) were reported with canagliflozin 100 mg and canagliflozin 300 mg, respectively, compared to the control group (-3.0%) (see sections 4.2 and 4.4).

Metformin

Table 2 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 2: The frequency of metformin adverse reactions identified from clinical trial and postmarketing data

System organ class Frequency	Adverse reaction
<i>Metabolism and nutrition disorders</i>	
very rare	Lactic acidosis, Vitamin B ₁₂ deficiency ^a
<i>Nervous system disorders</i>	
common	Taste disturbance
<i>Gastrointestinal disorders</i>	
very common	Gastro-intestinal symptoms ^b
<i>Skin and subcutaneous tissue disorders</i>	
very rare	Erythema, Pruritis, Urticaria
<i>Hepatobiliary disorders</i>	
very rare	Liver function test abnormal, Hepatitis

^a Long-term treatment with metformin has been associated with a decrease in vitamin B₁₂ absorption, which may very rarely result in clinically significant vitamin B₁₂ deficiency (e.g., megaloblastic anaemia).

^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 1600 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 oral 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 antihyperglycemic 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%.

Clinical efficacy and safety

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

A total of 10,285 patients with type 2 diabetes participated in nine 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, 4% Black, and 8% other groups. 16% of patients were Hispanic. Approximately 58% of patients were male. Patients had an overall mean age of 59.6 years (range 21 years to 96 years), with 3,082 patients ≥ 65 years of age and 510 patients ≥ 75 years of age. 58% of patients had a body mass index (BMI) ≥ 30 kg/m².

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 3). 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.

Table 3: Efficacy results from placebo-controlled clinical studies^a

Dual therapy with metformin (26 weeks)			
	Canagliflozin + metformin		Placebo + metformin
	100 mg (N=368)	300 mg (N=367)	(N=183)
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

^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).

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 glycemic 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 4.

Table 4: 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 5). 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 5: 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
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^a Intent-to-treat population using last observation in study prior to glycaemic rescue therapy.

^b $p < 0.05$.

^c Not applicable.

^d $p < 0.001$.

Special populations

In two studies conducted in special populations (older patients and patients with or at high risk for cardiovascular disease), canagliflozin was added to patients' current stable diabetes treatments (diet, monotherapy, or combination therapy).

Older patients

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).

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.

Cardiovascular safety

A pre-specified interim meta-analysis was conducted of adjudicated major cardiovascular events in the phase 2 and 3 clinical studies in 9,632 patients with type 2 diabetes, including 4,327 patients (44.9%) with cardiovascular disease or at high risk for cardiovascular disease who are participating in an

ongoing cardiovascular study. The hazard ratio for the composite primary endpoint (time to event of cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, and unstable angina requiring hospitalisation) for canagliflozin (both doses pooled) *versus* combined active and placebo comparators was 0.91 (95% CI: 0.68; 1.22); therefore, there was no evidence of an increase in cardiovascular risk with canagliflozin relative to comparators. The hazard ratios for the canagliflozin 100 mg and 300 mg once daily doses were similar.

Blood pressure

In an analysis of four 26-week, placebo-controlled studies (N=2,313), treatment with canagliflozin 100 mg and 300 mg once daily 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 once daily and 300 mg once daily 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 once daily, respectively.

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 diabetes-related 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/1000 mg, 150 mg/850 mg, and 150 mg/1000 mg combination tablets are bioequivalent to co-administration of corresponding doses of canagliflozin and metformin as individual tablets.

Administration of Vokanamet 150 mg/1000 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 intolerance 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 \pm 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 119 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

Patients with 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 Cockcroft-Gault equation) compared to healthy subjects. The study included 8 subjects with normal renal function (CrCl \geq 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 renal disease (ESRD) 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 ESRD subjects and healthy subjects.

Canagliflozin was negligibly removed by haemodialysis.

Patients with 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 (\geq 65 years old)

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

Studies characterising the pharmacokinetics of canagliflozin in paediatric patients have not been conducted.

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 trials, 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 Pre-clinical 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 \geq 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 1 through day 90 postnatal did not show increased sensitivity compared to effects observed in adult rats. However, dilatation of the renal pelvis was noticed with a No Observed Effect Level (NOEL) at exposures 2.4 times and 0.6 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-fetal 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 300/2000 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

150 mg/1000 mg:
Macrogol (3350)
Polyvinyl alcohol
Talc
Titanium dioxide (E171)
Iron oxide red (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 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
180 (3 x 60) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 April 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://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**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

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/1000 mg film-coated tablets
Vokanamet 150 mg/850 mg film-coated tablets
Vokanamet 150 mg/1000 mg film-coated tablets
canagliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains canagliflozin hemihydrate, equivalent to 50 mg canagliflozin, and 850 mg metformin hydrochloride.

Each film-coated tablet contains canagliflozin hemihydrate, equivalent to 50 mg canagliflozin, and 1000 mg metformin hydrochloride.

Each film-coated tablet contains canagliflozin hemihydrate, equivalent to 150 mg canagliflozin, and 850 mg metformin hydrochloride.

Each film-coated tablet contains canagliflozin hemihydrate, equivalent to 150 mg canagliflozin, and 1000 mg metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 film-coated tablets

60 film-coated tablets

60 film-coated tablets. Component of a 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/1/14/918/001 (50 mg/850 mg - 20 tablets)
EU/1/14/918/002 (50 mg/850 mg - 60 tablets)
EU/1/14/918/003 (50 mg/850 mg - 180 tablets)
EU/1/14/918/004 (50 mg/1000 mg - 20 tablets)
EU/1/14/918/005 (50 mg/1000 mg - 60 tablets)
EU/1/14/918/006 (50 mg/1000 mg - 180 tablets)
EU/1/14/918/007 (150 mg/850 mg - 20 tablets)
EU/1/14/918/008 (150 mg/850 mg - 60 tablets)
EU/1/14/918/009 (150 mg/850 mg - 180 tablets)
EU/1/14/918/010 (150 mg/1000 mg - 20 tablets)
EU/1/14/918/011 (150 mg/1000 mg - 60 tablets)
EU/1/14/918/012 (150 mg/1000 mg - 180 tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

vokanamet 50 mg/850 mg
vokanamet 50 mg/1000 mg
vokanamet 150 mg/850 mg
vokanamet 150 mg/1000 mg

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/1000 mg film-coated tablets
Vokanamet 150 mg/850 mg film-coated tablets
Vokanamet 150 mg/1000 mg film-coated tablets
canagliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains canagliflozin hemihydrate, equivalent to 50 mg canagliflozin, and 850 mg metformin hydrochloride.

Each film-coated tablet contains canagliflozin hemihydrate, equivalent to 50 mg canagliflozin, and 1000 mg metformin hydrochloride.

Each film-coated tablet contains canagliflozin hemihydrate, equivalent to 150 mg canagliflozin, and 850 mg metformin hydrochloride.

Each film-coated tablet contains canagliflozin hemihydrate, equivalent to 150 mg canagliflozin, and 1000 mg metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

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 tablets)
EU/1/14/918/002 (50 mg/850 mg - 60 tablets)
EU/1/14/918/003 (50 mg/850 mg - 180 tablets)
EU/1/14/918/004 (50 mg/1000 mg - 20 tablets)
EU/1/14/918/005 (50 mg/1000 mg - 60 tablets)
EU/1/14/918/006 (50 mg/1000 mg - 180 tablets)
EU/1/14/918/007 (150 mg/850 mg - 20 tablets)
EU/1/14/918/008 (150 mg/850 mg - 60 tablets)
EU/1/14/918/009 (150 mg/850 mg - 180 tablets)
EU/1/14/918/010 (150 mg/1000 mg - 20 tablets)
EU/1/14/918/011 (150 mg/1000 mg - 60 tablets)
EU/1/14/918/012 (150 mg/1000 mg - 180 tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

LABEL (multipack)

1. NAME OF THE MEDICINAL PRODUCT

Vokanamet 50 mg/850 mg film-coated tablets
Vokanamet 50 mg/1000 mg film-coated tablets
Vokanamet 150 mg/850 mg film-coated tablets
Vokanamet 150 mg/1000 mg film-coated tablets
canagliflozin/metformin hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains canagliflozin hemihydrate, equivalent to 50 mg canagliflozin, and 850 mg metformin hydrochloride.

Each film-coated tablet contains canagliflozin hemihydrate, equivalent to 50 mg canagliflozin, and 1000 mg metformin hydrochloride.

Each film-coated tablet contains canagliflozin hemihydrate, equivalent to 150 mg canagliflozin, and 850 mg metformin hydrochloride.

Each film-coated tablet contains canagliflozin hemihydrate, equivalent to 150 mg canagliflozin, and 1000 mg metformin hydrochloride.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

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 tablets)
EU/1/14/918/006 (50 mg/1000 mg - 180 tablets)
EU/1/14/918/009 (150 mg/850 mg - 180 tablets)
EU/1/14/918/012 (150 mg/1000 mg - 180 tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

vokanamet 50 mg/850 mg
vokanamet 50 mg/1000 mg
vokanamet 150 mg/850 mg
vokanamet 150 mg/1000 mg

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Vokanamet 50 mg/850 mg film-coated tablets
Vokanamet 50 mg/1000 mg film-coated tablets
Vokanamet 150 mg/850 mg film-coated tablets
Vokanamet 150 mg/1000 mg film-coated tablets

canagliflozin/metformin hydrochloride

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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
2. What you need to know before you take Vokanamet
3. How to take Vokanamet
4. Possible side effects
5. How to store Vokanamet
6. Contents of the pack and other information

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 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 kidney or liver problems
- 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 diabetic ketoacidosis (a complication of diabetes with high blood sugar, rapid weight loss, feeling sick [nausea], or being sick [vomiting])
- 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

Talk to your doctor, pharmacist or nurse before taking this medicine, and during treatment:

- about what you can do to prevent dehydration
- if you have type 1 diabetes (your body does not produce any insulin). 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, contact a doctor or the nearest hospital straight away. These symptoms could be a sign of "diabetic ketoacidosis" – a 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 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".

Kidney function

Your kidneys will be tested by a blood test before you start taking and while you are taking this medicine.

Look out for side effects

Lactic acidosis is a medical emergency and must be treated in a hospital. If you experience some of the signs of lactic acidosis which include feeling sick (nausea) or being sick (vomiting), stomach ache, severe weakness, muscle cramps, unexplained weight loss, rapid breathing, or feeling cold or uncomfortable, **stop taking Vokanamet immediately and contact a doctor or go to the nearest hospital straight away.** See section 4.

Operations and X-rays

Tell your doctor you are taking Vokanamet if you are going to have:

- an operation under general, spinal, or peridural anaesthetic. You may need to stop taking Vokanamet for a couple of days before and after the operation.
- an X-ray where you will be injected with a dye. You will need to stop taking Vokanamet before, or at the time of the X-ray and for 2 or more days after. Before taking Vokanamet again, your kidney function should be tested.

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.

Other medicines and 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.

In particular, tell your doctor if you are taking any of the following medicines:

- 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 used to lower your blood pressure (anti-hypertensives), including diuretics (medicines used to remove levels of excess water in the body, also known as water tablets) since this medicine can also lower your blood pressure by removing levels of excess water in the body. Possible signs of losing too much fluid from your body are listed under “Dehydration” in section 4.
- St. John's wort (a herbal medicine used to treat depression)
- carbamazepine, phenytoin, or phenobarbital (medicines used to control seizures)
- 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”.
- iodinated contrast agents (medicines used during an X-ray). See section “Operations and X-rays”.
- 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.

Vokanamet with alcohol

Avoid consumption of large amounts of alcohol, or medicines containing alcohol, when taking this medicine. This is because you are at an increased risk of getting a build-up of lactic acid in your blood (lactic acidosis) if you have too much alcohol. This is more likely if you are already fasting, have malnutrition, or liver problems. See section “Look out for side effects” and section 4.

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.

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 at least a half glass of 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

If you take more of this medicine than you should, talk to a doctor straight away.

If you forget to take Vokanamet

- If you forget to take a dose, take it as soon as you remember. However, if it is nearly 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 immediately and contact a doctor or go to the nearest hospital straight away if you have any of the following serious side effects:

Lactic acidosis (very rare, may affect up to 1 in 10,000 people)

- too much lactic acid in your blood (lactic acidosis). This happens more often in people with kidney problems. Lactic acidosis may also be caused by excessive alcohol intake or prolonged fasting.

Possible signs of lactic acidosis are:

- feeling sick (nausea) or being sick (vomiting)
- stomach ache
- severe weakness
- muscle cramps
- unexplained weight loss
- rapid breathing
- feeling cold or uncomfortable.

Stop taking Vokanamet and contact a doctor as soon as possible if you have any of the following serious side effects:

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.

Contact a doctor or the nearest hospital straight away if you have any of the following side effects:

Diabetic ketoacidosis (rare, may affect up to 1 in 1,000 people)

These are the signs of diabetic ketoacidosis (see also section 2 Warnings and precautions):

- 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.

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.

Other side effects when taking canagliflozin alone:

Very common

- vaginal yeast infection.

Common (may affect up to 1 in 10 people)

- rash or redness of the penis or foreskin (yeast infection)
- urinary tract infections
- 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

- 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).

Not known

- severe allergic reaction (may include swelling of the face, lips, mouth, tongue, or throat that may lead to difficulty breathing or swallowing).

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)
- very rare: decreased vitamin B₁₂ levels (may cause anaemia – low count of red blood cells), 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 50 mg of canagliflozin and 850 mg of metformin hydrochloride.
 - Each 50 mg/1000 mg tablet contains 50 mg of canagliflozin and 1000 mg of metformin hydrochloride.
 - Each 150 mg/850 mg tablet contains 150 mg of canagliflozin and 850 mg of metformin hydrochloride.
 - Each 150 mg/1000 mg tablet contains 150 mg of canagliflozin and 1000 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), polyvinyl alcohol, talc, titanium dioxide (E171), iron oxide red (E172) and iron oxide black (E172).
 - 50 mg/1000 mg tablets: macrogol (3350), polyvinyl alcohol, talc, titanium dioxide (E171), iron oxide yellow (E172), and iron oxide red (E172).
 - 150 mg/850 mg tablets: macrogol (3350), polyvinyl alcohol, talc, titanium dioxide (E171), and iron oxide yellow (E172).
 - 150 mg/1000 mg tablets: macrogol (3350), polyvinyl 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/1000 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/1000 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, 60, and 180 tablets (3 bottles containing 60 tablets each).

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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Manufacturer

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This leaflet was approved in {month YYYY}.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>.