Summary of Risk Management Plan for VOKANAMET (Canagliflozin/Metformin Hydrochloride Fixed-dose Combination)

This is a summary of the risk management plan (RMP) for VOKANAMET. The RMP details important risks of VOKANAMET, how these risks can be minimized, and how more information will be obtained about VOKANAMET's risks and uncertainties (missing information).

VOKANAMET's summary of product characteristics (SmPC) and its package leaflet (PL) provide essential information to healthcare professionals and patients on how VOKANAMET should be used.

This summary of the RMP for VOKANAMET should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of VOKANAMET's RMP.

I. The Medicine and What it is Used For

VOKANAMET is authorized for treatment of adults with insufficiently controlled type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise (see SmPC for the full indication). VOKANAMET is a fixed-dose combination (FDC) containing canagliflozin and metformin as two different active substances. These are two medicines that work together in different ways to lower blood glucose (sugar) levels and can help prevent heart disease in adults with T2DM. It can be used by itself, or in combination with other medicinal products for the treatment of diabetes. It also can be used in patients already being treated with the combination of canagliflozin and metformin as separate tablets. VOKANAMET is given as an oral film-coated tablet (canagliflozin/metformin hydrochloride [HCl] 50 mg/850 mg, 50 mg/1000 mg, 150 mg/850 mg, 150 mg/1000 mg).

Further information about the evaluation of VOKANAMET's benefits can be found in VOKANAMET's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/vokanamet

II. Risks Associated With the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of VOKANAMET, together with measures to minimize such risks and the proposed studies for learning more about VOKANAMET's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of VOKANAMET, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A. List of Important Risks and Missing Information

Important risks of VOKANAMET are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of VOKANAMET. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	Diabetic ketoacidosis with atypical presentation Lactic acidosis
Important potential risks	None
Missing information	Use in pregnancy Use in nursing mothers

II.B. Summary of Important Risks

Important Identified Risk: Diabetic ketoacidosis with atypical presentation	
Evidence for linking the risk to the medicine	Diabetic ketoacidosis (DKA) has been reported during postmarketing experience with canagliflozin in T2DM patients, including cases with fatal outcomes. An atypical presentation (blood glucose values less than 13.9 mmol/L [250 mg/dL]) has been observed during postmarketing surveillance in cases of DKA for canagliflozin and across the class of sodium-glucose co-transporter-2 (SGLT2) inhibitors. Cases of ketoacidosis have occurred during off-label use of SGLT2 inhibitors in type 1 diabetes mellitus (T1DM) patients and in T1DM clinical trials (EMA, 2017). In an 18-week Phase 2 trial in subjects with T1DM randomized to either canagliflozin or placebo (DIA2004), the frequency of DKA was higher than that observed in T2DM clinical trials.
Risk factors and risk groups	The available clinical trial data suggest that patients diagnosed as having T2DM or misdiagnosed as T2DM (eg, T1DM, latent autoimmune diabetes of adulthood), and who have a low beta-cell reserve, are unable to produce sufficient insulin to suppress hepatic ketogenesis and peripheral lipolysis. In the setting of known DKA precipitating factors, such as an acute illness (and associated increase in insulin resistance), these patients can develop DKA. The increased rate of DKA in the CREDENCE trial was observed predominantly in subjects in the lowest eGFR stratum; which included subjects with a longer duration of diabetes, higher proportion of insulin use, and higher baseline glycosylated hemoglobin (HbA1c) than the overall population.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.8 and PL Section 4. • Recommendations regarding appropriate dosing and patient management (including advice on discontinuation and restart) are provided in SmPC Section 4.4; • Advice to patients who have DKA, including a warning that canagliflozin/metformin HCl FDC should not be used to treat this condition, is provided in PL Sections 2 and 4; • Advice on when to suspect DKA is provided in SmPC Section 4.4 and PL Sections 2 and 4; • Description of factors that may predispose patients to DKA, and advice on use in patients at higher risk for DKA are provided in SmPC Section 4.4 and PL Section 2; • Warning not to use canagliflozin/metformin HCl FDC in patients with T1DM is provided in SmPC Section 4.4 and PL Section 2. Additional risk minimization measures: • Direct Healthcare Professional Communication.
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaire; • Adjudication of DKA events from ongoing clinical trials by an independent blinded committee. Additional pharmacovigilance activities: • PASS: Retrospective Drug Utilization Study. See Section II.C of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Lactic acidosis	
Evidence for linking the risk to the medicine	Evidence for lactic acidosis from metformin is based on the literature, including case reports, review of clinical trials and observational studies, as well as metformin drug labels. Lactic acidosis is a rare, but serious 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 (Metformin SmPC, 2015). Lactic acidosis has been reported in Phase 3/4 clinical trials when canagliflozin was given to subjects who were on a background of metformin, but at a lower incidence than observed in the comparator group.
Risk factors and risk groups	Risk factors include conditions that may be associated with or promote hypoxia, including heart failure, tissue hypoxia, respiratory failure, defective lactate clearance (alcohol abuse, and liver failure), renal impairment, renal or hepatic insufficiency. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age.
Risk minimization measures	Routine risk communication: • SmPC Section 4.2; • SmPC Section 4.4 and PL Section 2; • SmPC Section 4.8 and PL Section 4. • Contraindication in patients with an increased risk of lactic acidosis is described in SmPC Section 4.3 and PL Section 2, including detailed list of conditions; • Patient management of dehydration is described in SmPC Section 4.4 and PL Section 2; • Recommendations regarding concomitant use with medicinal products that acutely impair renal function or cause lactic acidosis or its use in patients with risk factors for lactic acidosis are provided in SmPC Section 4.4; • Patient management of lactic acidosis, including guidance on diagnosis, discontinuation, and need for medical attention, is described in SmPC Section 4.4 and PL Section 4; • Recommendations for monitoring of renal function is provided in SmPC Section 4.4 and PL Section 4; • Advice on concomitant use with alcohol, medicinal products containing alcohol, cationic drugs that are eliminated by renal tubular secretion, iodinated contrast agents, and medicinal products that can adversely affect renal function is provided in SmPC Section 4.5 and PL Section 2; • Advice on patient management of overdose, including how to remove lactate and metformin (hemodialysis), is provided in SmPC Section 4.9. Additional risk minimization measures: • None.
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaire.

Missing Information: Use in pregnancy	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.6 and PL Section 2. • Recommendation regarding use of canagliflozin/metformin HCl FDC during pregnancy is provided in SmPC Section 4.6 and PL Section 2. Additional risk minimization measures: • None.

Missing Information: Use in nursing mothers	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.6 and PL Section 2. • Recommendation regarding use of canagliflozin/metformin HCl FDC during breast-feeding is provided in SmPC Section 4.6 and PL Section 2. Additional risk minimization measures: • None.

II.C. Post-authorization Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of VOKANAMET.

II.C.2. Other Studies in Post-authorization Development Plan

Post-authorization Safety Study: To describe the time-trend of canagliflozin utilization in patients with T1DM using real-world databases in European countries with high cumulative exposure, including the United Kingdom, Spain, Italy, and Belgium.

Purpose of the study: To describe the time-trend of drug utilization of canagliflozin among patients with T1DM in a European setting.