Summary of risk management plan for Evrenzo (roxadustat)

This is a summary of the RMP for EVRENZO. The RMP details important risks of EVRENZO, how these risks can be minimised and how more information will be obtained about the risks EVRENZO.

The EVRENZO SmPC gives essential information to healthcare professionals and patients on how EVRENZO should be used.

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

I. The medicine and what it is used for

EVRENZO is authorised for the treatment of adult patients with anaemia associated with CKD. It contains roxadustat as the active substance and it is taken orally.

Further information about the evaluation of the benefits of EVRENZO can be found in the EPAR of EVRENZO, including in its plain-language summary, available on the EMA website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/evrenzo

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of EVRENZO, together with measures to minimise such risks and the proposed studies for learning more about the risks of EVRENZO, are outlined below.

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

- Specific information, such as warnings, precautions and advice on correct use, are in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised 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 (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed 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 EVRENZO are risks that need special risk management activities to further investigate or minimise 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 EVRENZO.
- Potential risks are concerns for which an association with the use of EVRENZO 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 EVRENZO that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Thrombotic vascular events Seizures Sepsis
Important potential risks	Serious infections
Missing information	Data in pregnant and breastfeeding patients

II.B Summary of important risks

Important identified risk: Thrombotic vascular events	
Evidence for linking the risk to the medicine	In clinical trials, thrombotic vascular events were more frequently seen with roxadustat treatment than with placebo and comparator. VAT events were the most frequent thrombotic vascular events experienced. In (NDD)-CKD safety pool; vascular access thrombosis events were more frequent in the roxadustat group than in the placebo group. In the DD-CKD safety pool, VAT events were more frequent in the roxadustat group than in the comparator group. The events of DVT and PE evaluated together showed more frequent events for roxadustat than placebo in the NDD pool. In the DD pool, DVT and PE events were greater for roxadustat than the comparators.

Risk factors and risk groups	In the DD-CKD safety pool, vascular access thrombosis occurred more commonly in the period shortly after treatment initiation in patients already on dialysis with previous erythropoietin-stimulating agent use and was also more commonly associated with increased and/or rapid rise of haemoglobin levels. No specific association between increased and/or rapid rise of haemoglobin and DVT or PE was found. General risk factors for thrombotic vascular events include history of thromboembolic events, hypercoagulable state, technical issues related to AV access creation, type of vascular access (graft or fistula), AV access stenosis, cannulation injury/more frequent cannulation (e.g., daily haemodialysis), infiltration/haematoma formation, intimal lesion or hyperplasia, pseudoaneurysm at the AV access site, presence of malignancy, and treatment with chemotherapy for cancer.
Risk minimisation measures	Routine risk communication: Special warnings and precautions for use and Adverse reactions sections of the SmPC (section 4.4 and 4.8). Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for haemoglobin monitoring are included in the Special warnings and precautions for use section of the SmPC.

Abbreviations: AV = Arteriovenous; CKD = Chronic Kidney Disease; DVT = deep vein thrombosis; NDD = Non Dialysis Dependent; DD = Dialysis Dependent; PE = Pulmonary embolus; SmPC = summary of product characteristics; VAT = Vascular Access Thrombosis

Important identified risk: Sepsis	
Evidence for linking the risk to the medicine	In the NDD-CKD safety pool, Sepsis was reported at a higher incidence in the roxadustat group compared to the placebo group; Sepsis was one of the most commonly reported serious infections in the pool. Fatal Sepsis was more frequent with roxadustat than placebo and were more pronounced in patients with low eGFR (< 10 mL/min/1.73m^2) or who recently initiated dialysis. In the DD-CKD safety pool, the incidence rate of Sepsis and Fatal Sepsis events were similar between roxadustat and comparators. Sepsis was one of the most commonly reported serious infections in the pool.

Risk factors and risk groups	Patients with low eGFR levels (< 10 mL/min/1.73 m^2) who are not on dialysis or who recently initiated dialysis (within 4 months). General risk factors: intensive care admission, advanced age, immunodeficiency, diabetes mellitus, obesity, malignancy, history of recent hospitalizations, alcohol abuse and malnutrition. In patients with CKD, additional risk factors include decreased vaccine responsiveness, impaired immune response, loss of cutaneous barriers (e.g., oedema, dialysis catheters, needle sticks in AVF/AVG), type of dialysis (haemodialysis or peritoneal dialysis), and type of vascular access (graft or fistula) for haemodialysis subjects.
Risk minimisation measures	Routine risk communication: Warnings & precautions section of the SmPC. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for monitoring signs and symptoms of infection are included in Special warnings and precautions for use section 4.4 of the SmPC.

Important identified risk: Seizure	
Evidence for linking the risk to the medicine	In the NDD-CKD safety pool, events of seizure were more frequent in the roxadustat group than in the placebo group. In the DD-CKD safety pool, events of seizure were more frequent in the roxadustat group than in the comparator group.
Risk factors and risk groups	No specific risk factors or risk groups for seizure were observed in the roxadustat clinical development programme. General risk factors include history of seizures, head trauma or neurologic disease, stroke, brain tumours, renal failure, advanced age, genetic predisposition, alcohol or drug withdrawal, drug intoxication, electrolyte imbalances, hypoglycaemia, nonketotic hyperglycaemia, hypoxia, hyperthyroidism, dialysis disequilibrium syndrome and severe hypertension.

Risk minimisation measures	Routine risk communication: Special warnings and precautions for use, Effects on ability to drive and use machines and Adverse reactions sections of the SmPC (sections 4.4, 4.7 and 4.8). Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for monitoring the presence of premonitory neurologic symptoms following treatment initiations are included in the Special warnings and precautions for use section of the SmPC (Section 4.4).

Important potential risk: Serious infections	
Evidence for linking the risk to the medicine	In the NDD-CKD safety pool, SAEs of MedDRA SOC Infections & Infestations were reported at a higher incidence in the roxadustat group compared to the placebo group; however, adjusted incidence rates were similar between treatment groups. The most commonly reported serious infections were pneumonia, sepsis, urinary tract infection. Fatal infections were more frequent with roxadustat than placebo and were more pronounced in patients with low eGFR (< 10 mL/min/1.73m^2) or who recently initiated dialysis. In the DD-CKD safety pool, the incidence rate of SAE and fatal events of infections were similar between roxadustat and comparators. The most commonly reported serious infections were pneumonia and urinary tract infection. In a subset of patients in the DD-CKD safety pool who initiated roxadustat within 4 months of starting dialysis (ID-DD), the incidence rate of SAEs of infection were slightly higher in the roxadustat group compared to the comparator group. In this ID-DD subset, fatal infections were reported more frequently in the roxadustat group compared to the comparator group.

Risk factors and risk groups	Patients with low eGFR levels (< 10 mL/min/1.73 m^2) who are not on dialysis or who recently initiated dialysis (within 4 months). General risk factors: intensive care admission, advanced age, immunodeficiency, diabetes mellitus, obesity, malignancy, history of recent hospitalizations, alcohol abuse and malnutrition. In patients with CKD, additional risk factors include decreased vaccine responsiveness, impaired immune response, loss of cutaneous barriers (e.g., oedema, dialysis catheters, needle sticks in AVF/AVG), type of dialysis (haemodialysis or peritoneal dialysis) and type of vascular access (graft or fistula) for haemodialysis subjects.
Risk minimisation measures	Routine risk communication: Warnings & Precautions section of the SmPC. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for monitoring signs and symptoms of infection are included in Special warnings and precautions for use section 4.4 of the SmPC.

Abbreviations: AVF = Arteriovenous Fistula; AVG = Arteriovenous Graft; CKD = Chronic Kidney Disease; DD = Incident Dialysis-Dialysis dependent; DD-CKD = Dialysis dependent Chronic Kidney Disease; eGFR = estimated Glomerular Filtration Rate; NDD-CKD = Non Dialysis dependent Chronic Kidney Disease; - SAE = Serious Adverse Event; SmPC = Summary of Product Characteristics; SOC = System Organ Class;

Missing Information: Data in Pregnant and Breastfeeding Patients	
Risk minimization measures	Risk communication: • Contraindication (SmPC 4.3) • Special warnings and precautions (SmPC section 4.4) • Fertility, pregnancy and lactation (SmPC section 4.6) • Patient leaflet section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: • Women of childbearing potential must use highly effective contraception during treatment and for at least one week after the last dose of roxadustat. If pregnancy occurs while roxadustat is being administered, treatment should be discontinued and switched to alternative treatments (SmPC 4.4 and 4.6). Other routine risk minimization measures beyond the Product information: None

II.C Postauthorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of marketing authorisation or specific obligation for EVRENZO.

II.C.2 Other studies in postauthorization development plan

There are no studies required for EVRENZO.