Prescribing Information: EVRENZO™▼ (roxadustat) film-coated tablets

Presentations: EVRENZO film-coated tablets containing 20 mg, 50 mg, 70 mg, 100 mg, and 150 mg roxadustat.

Indications: Treatment of adult patients with symptomatic anaemia associated with chronic kidney disease (CKD).

Posology and Administration: Treatment should be initiated by a physician experienced in the management of anaemia. All other causes of anaemia should be evaluated prior to initiating therapy with EVRENZO and when increasing the dose. EVRENZO must be taken orally three times weekly and not on consecutive days. The tablets are taken orally with/without food, swallowed whole and should not be chewed, broken or crushed. EVRENZO can be taken before or after dialysis (see SPC section 5.2). Individualise dose to achieve and maintain target haemoglobin (Hb) levels of 10–12 g/dL. Treatment should not continue beyond 24 weeks if a clinically meaningful increase in Hb levels is not achieved. Starting dose: Ensure adequate iron stores prior to initiation. Patients not currently/previously treated with an erythropoiesis-stimulating agent (ESA): Recommended starting dose: Patients <100kg: 70mg three times weekly. Patients ≥100kg: 100mg three times weekly. Patients converting from an ESA: Patients on ESA treatment can be converted to roxadustat. *Dialysis patients stable on ESA*: only consider conversion if clinically valid reasons exist. *Non-dialysis patients stable on ESA*: conversion not studied, only consider on benefit-risk to patient. The recommended starting dose is based on the average prescribed ESA dose in the 4 weeks before conversion. The first roxadustat dose should replace the next scheduled ESA dose. See Table 1. in the SPC. Maximum recommended dose: Patients not on dialysis do not exceed a roxadustat dose of 3 mg/kg body weight or 300 mg three times weekly, whichever is lower. Patients on dialysis do not exceed a roxadustat dose of 3 mg/kg body weight or 400 mg three times weekly, whichever is lower. Dose adjustments and Hb monitoring: The individualised maintenance dose is 20– 400 mg three times weekly. Monitor Hb every 2 weeks until a level of 10-12 g/dL is reached and stabilised, then every 4 weeks or as clinically indicated. The dose of roxadustat can be adjusted stepwise up or down from the starting dose 4 weeks after treatment start, then every 4 weeks except if the Hb increases by >2 g/dL, in which case the dose should be reduced by one step immediately. When adjusting the dose, consider the current Hb level and the recent rate of change in Hb level over the past 4 weeks, and follow the dose adjustment steps in Table 2 in SPC section 4.2. If dose reduction is required for a patient on the lowest dose, reduce the dose frequency to twice a week. If further dose reduction is needed, the frequency may be reduced to once weekly. Maintenance dose: After stabilisation of target Hb levels, monitor Hb levels regularly and follow dose adjustment rules. Consider alternative explanations in patients with inadequate Hb response (see SPC section 4.2). Patients starting dialysis while on roxadustat treatment: No specific dose adjustments required. Follow normal dose adjustment rules. Concomitant roxadustat treatment with inducers or inhibitors: When initiating/discontinuing concomitant treatment with strong inhibitors or inducers of CYP2C8, or inhibitors of UGT1A9, monitor Hb levels routinely and follow dose adjustment rules. Missed dose: If there is >1 day until the next dose, the missed dose must be taken as soon as possible. If ≤ one day remains before the next dose, skip the missed dose. Then resume the regular dosing schedule. Elderly: No adjustment of starting dose (see SPC section 5.2). Patients with hepatic impairment: Mild hepatic impairment: No adjustment of starting dose. Moderate hepatic impairment: Caution is recommended. Reduce starting dose by half or to the level closest to half the starting dose. Severe hepatic impairment: Not recommended (see SPC sections 4.4 & 5.2). Paediatric population: No data are available in patients < 18 years of age.

Contraindications: EVRENZO is contraindicated in the following conditions: Hypersensitivity to the active substance, peanut, soya, or to any of the excipients listed in section 6.1 of the SPC; Third trimester of pregnancy (see sections 4.4 & 4.6 of the SPC); Breastfeeding (see section 4.6 of the SPC).

Warnings and precautions: Cardiovascular and mortality risk: Overall, the cardiovascular and mortality risk for treatment with roxadustat has been estimated to be comparable to the cardiovascular and mortality risk for ESA therapy based on data from direct comparison of both therapies (see SPC section 5.1). Since, for patients with anaemia associated with CKD and not on dialysis, this risk could not be estimated with sufficient confidence versus placebo, a decision to treat these patients with roxadustat should be based on similar considerations that would be applied before treating with an ESA . Further, several contributing factors have been identified that may impose this risk, including treatment non-responsiveness, and converting stable ESA treated dialysis patients (see SPC sections 4.2 and 5.1). In the case of non-responsiveness, treatment with roxadustat should not be continued beyond 24 weeks after the start of treatment (see SPC section 4.2). Conversion of dialysis patients otherwise stable on ESA treatment is only to be considered when there is a valid clinical reason (see SPC section 4.2). For stable ESA treated patients with anaemia associated with CKD and not on dialysis,

this risk could not be estimated as these patients have not been studied. A decision to treat these patients with roxadustat should be based on a benefit risk consideration for the individual patient. Thrombotic vascular events: The reported risk of thrombotic vascular events (TVEs) should be carefully weighed against the benefits to be derived from treatment with roxadustat particularly in patients with pre-existing risk factors for TVE, including obesity and prior history of TVEs (e.g., deep vein thrombosis [DVT] and pulmonary embolism [PE]). Deep vein thrombosis was reported as common and pulmonary embolism as uncommon amongst the patients in clinical studies. The majority of DVT and PE events were serious. Vascular access thrombosis (VAT) was reported as very common amongst the CKD patients on dialysis in clinical studies (see SPC section 4.8). In CKD patients on dialysis, rates of VAT in roxadustat-treated patients were highest in the first 12 weeks following initiation of treatment, at Hb values more than 12 g/dL and in the setting of Hb rise of more than 2 g/dL over 4 weeks. It is recommended to monitor Hb levels and adjust the dose using the dose adjustment rules (see Table 2) to avoid Hb levels of more than 12 g/dL and Hb rise of more than 2 g/dL over 4 weeks. Patients with signs and symptoms of TVEs should be promptly evaluated and treated according to standard of care. The decision to interrupt or discontinue treatment should be based on a benefit-risk consideration for the individual patient. Seizures: Seizures were reported as common amongst the patients in clinical studies receiving roxadustat (see SPC section 4.8). Roxadustat should be used with caution in patients with a history of seizures (convulsions or fits), epilepsy or medical conditions associated with a predisposition to seizure activity such as central nervous system (CNS) infections. The decision to interrupt or discontinue treatment should be based on a benefit-risk consideration of the individual patient. Serious infections: The most commonly reported serious infections were pneumonia and urinary tract infections. Patients with signs and symptoms of an infection should be promptly evaluated and treated according to standard of care. Sepsis: Sepsis was one of the most commonly reported serious infections and included fatal events. Patients with signs and symptoms of sepsis (e.g., an infection that spreads throughout the body with low blood pressure and the potential for organ failure) should be promptly evaluated and treated according to standard of care. Inadequate response to therapy: Inadequate response to therapy with roxadustat should prompt a search for causative factors. Nutrient deficiencies should be corrected. Intercurrent infections, occult blood loss, haemolysis, severe aluminium toxicity, underlying haematologic diseases or bone marrow fibrosis may also compromise the erythropoietic response. A reticulocyte count should be considered as part of the evaluation. If typical causes of non-response are excluded, and the patient has reticulocytopenia, an examination of the bone marrow should be considered. In the absence of an addressable cause for an inadequate response to therapy, Evrenzo should not be continued beyond 24 weeks of therapy. Hepatic impairment: Caution is warranted when roxadustat is administered to patients with moderate hepatic impairment (Child-Pugh class B). Evrenzo is not recommended for use in patients with severe hepatic impairment (Child-Pugh class C) (see SPC section 5.2). Pregnancy and contraception: Roxadustat should not be initiated in women planning on becoming pregnant, during pregnancy or when anaemia associated with CKD is diagnosed during pregnancy. In such cases, alternative therapy should be started, if appropriate. If pregnancy occurs while roxadustat is being administered, treatment should be discontinued and alternative treatment started, if appropriate. Women of childbearing potential must use highly effective contraception during treatment and for at least one week after the last dose of EVRENZO (see SPC sections 4.3 and 4.6). Misuse: Misuse may lead to an excessive increase in packed cell volume. This may be associated with life-threatening complications of the cardiovascular system. Excipients: EVRENZO contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product. EVRENZO contains Allura Red AC aluminium lake (see SPC section 6.1) which may cause allergic reactions. EVRENZO contains traces of soya lecithin. Patients who are allergic to peanut or soya, should not use this medicinal product. Effects on ability to drive and use machines: Roxadustat has minor influence on the ability to drive and use machines. Caution should be exercised when driving or using machines.

Interactions: Effect of other medicinal products on roxadustat: *Phosphate binders and other products containing multivalent cations:* Roxadustat should be taken >1 hour after administration of phosphate binders or other medicinal products or supplements containing multivalent cations (not lanthanum carbonate) (see SPC section 4.2). *Modifiers of CYP2C8 or UGT1A9 activity:* Monitor Hb levels when initiating/ discontinuing concomitant treatment with gemfibrozil, probenecid, other strong inhibitors/inducers of CYP2C8 or other strong inhibitors of UGT1A9. Adjust the dose of roxadustat following dose adjustment rules based on Hb monitoring. (see SPC section 4.2). Effect of roxadustat on other medicinal products *OATP1B1 or BCRP Substrates*: Co administration of roxadustat with simvastatin in healthy subjects increased the AUC and C_{max} of simvastatin and simvastatin acid. The concentrations of simvastatin and simvastatin acid also increased when simvastatin was

administered 2 hours before or 4 or 10 hours after roxadustat. Co administration of roxadustat with rosuvastatin increased the AUC and C_{max} of rosuvastatin. Co administration of 200 mg of roxadustat with atorvastatin increased the AUC and C_{max} of atorvastatin. Interactions are also expected with other statins. Monitor for adverse reactions associated with statins and for the need of statin dose reduction. Roxadustat may increase the plasma exposure of other medicinal products that are substrates of BCRP or OATP1B1. Monitor for possible adverse reactions of co administered medicinal products and adjust dose accordingly. See SPC. Roxadustat and ESAs: It is not recommended to combine administration.

Pregnancy and lactation: There are no data on the use of roxadustat in pregnant women. Roxadustat is contraindicated in the third trimester of pregnancy and is not recommended during the first and second trimester. If pregnancy occurs during EVRENZO treatment, discontinue EVRENZO and switch to an alternative if appropriate. EVRENZO is contraindicated during breast-feeding. Fertility: The potential effects of roxadustat on male fertility in humans are unknown. At a maternally toxic dose, increased embryonic loss was observed. Women of childbearing potential must use highly effective contraception during treatment and for at least one week after the last dose.

Undesirable effects: Summary of the safety profile: The safety of EVRENZO was evaluated in 3542 non dialysis dependent (NDD) and 3353 dialysis dependent (DD) patients with anaemia and CKD who have received at least one dose of roxadustat. The most frequent (≥10%) adverse reactions associated with roxadustat are hypertension (13.9%), vascular access thrombosis (12.8%), diarrhoea (11.8%), peripheral oedema (11.7%), hyperkalaemia (10.9%) and nausea (10.2%). The most frequent (≥1%) serious adverse reactions associated with roxadustat were sepsis (3.4%), hyperkalaemia (2.5%), hypertension (1.4%) and deep vein thrombosis (1.2%). List of adverse reactions: Adverse reactions observed during clinical studies are listed in this section by frequency category and MedDRA system organ class. Frequency categories are defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). *Infections and infestations:* Common: Sepsis. *Metabolism and nutrition disorders:* Very common: Hyperkaelaemia. *Psychiatric disorders:* Common: Insomnia. *Nervous system disorders:* Common: Seizures, headache. *Vascular disorders:* Very common: Hypertension, vascular access thrombosis (VAT)*, Common: Deep vein thrombosis (DVT). *Gastrointestinal disorders:* Very common: Nausea, diarrhoea, Common: Constipation, vomiting. *Hepatobiliary disorders:* Uncommon: Hyperbilirubinaemia. *Respiratory, thoracic, mediastinal disorders:* Uncommon: Pulmonary embolism. *General disorders and administration site conditions:* Very common: Peripheral oedema.

*This adverse reaction is associated with CKD patients who were on dialysis while receiving roxadustat.

Description of selected adverse reactions. *Thrombotic vascular events:* In CKD patients not on dialysis, DVT events were uncommon, occurring in 1.0% (0.6 patients with events per 100 patient years of exposure) in the roxadustat group, and 0.2% (0.2 patients with events per 100 patient years of exposure) in the placebo group. In CKD patients on dialysis, DVT events occurred in 1.3% (0.8 patients with events per 100 patient years of exposure) in the roxadustat group and 0.3% (0.1 patients with events per 100 patient years of exposure) in the ESA group (see SPC section 4.4). In CKD patients not on dialysis, pulmonary embolism was observed in 0.4% (0.2 patients with events per 100 patient years of exposure) in the roxadustat group, compared to 0.2% (0.1 patients with events per 100 patient years of exposure) in the placebo group. In CKD patients on dialysis, pulmonary embolism was observed in 0.6% (0.3 patients with events per 100 patient years of exposure) in the roxadustat group, compared to 0.5% (0.3 patients with events per 100 patient years of exposure) in the ESA group (see SPC section 4.4). In CKD patients on dialysis, vascular access thrombosis was observed in 12.8% (7.6 patients with events per 100 patient years of exposure) in the roxadustat group, compared to 10.2% (5.4 patients with events per 100 patient years of exposure) in the ESA group (see SPC section 4.4). *Seizures:* In CKD patients not on dialysis, seizures occurred in 1.1% (0.6 patients with events per 100 patient years of exposure) in the roxadustat group, and 0.2% (0.2 patients with events per 100 patient years of exposure) in the placebo group (see SPC section 4.4). In CKD patients on dialysis, seizures occurred in 2.0% (1.2 patients with events per 100 patient years of exposure) in the roxadustat group, and 1.6% (0.8 patients with events per 100 patient years of exposure) in the ESA group (see SPC section 4.4). *Sepsis:* In CKD patients not on dialysis, sepsis was observed in 2.1% (1.3 patients with events per 100 patient years of exposure) in the roxadustat group, compared to 0.4% (0.3 patients with events per 100 patient years of exposure) in the placebo group. In patients on dialysis, sepsis was observed in 3.4% (2.0 patients with events per 100 patient years of exposure) in the roxadustat group, compared to 3.4% (1.8 patients with events per 100 patient years of exposure) in the ESA group (see SPC section 4.4).

Prescribers should consult the full summary of product characteristics in relation to other adverse reactions.

Overdose: Single supratherapeutic doses of roxadustat 5 mg/kg (up to 510 mg) in healthy subjects were associated with a transient increase in heart rate, an increased frequency of mild to moderate musculoskeletal pain, headaches, sinus tachycardia, and less commonly, low blood pressure (all non serious). Roxadustat overdose can elevate Hb levels above the desired level; manage with discontinuation or reduction of roxadustat dosage and careful monitoring and treatment as clinically indicated. Roxadustat and its metabolites are not significantly removed by haemodialysis.

Package Quantities, Basic NHS cost: EVRENZO (12 pack tablets): 20 mg = £59.24, 50 mg = £148.11, 70 mg = £207.35, 100 mg = £296.21, 150 mg = £444.32

Legal Classification: POM

Product licence numbers: EU/1/21/1574/001-005 (Northern Ireland); PLGB 00166/0427-0431 (Great Britain)

Marketing Authorisation Holder: Astellas Pharma Europe B.V. Sylviusweg 62, 2333 BE Leiden, The Netherlands (Northern Ireland); Astellas Pharma Ltd, SPACE, 68 Chertsey Road, Woking, Surrey GU21 5BJ (Great Britain)

Date of Preparation of Prescribing Information: August 2021

Document number: EVZ_2021_0043_UK

Further information available from: Astellas Pharma Ltd Medical Information: 0800 783 5018

For full prescribing information, please see the SPCs which may be found at https://www.emcmedicines.com/en-gb/northernireland/ (Northern Ireland or www.medicines.org.uk (Great Britain)

The hyperlinks on this page will take you to non-Astellas websites. Astellas does not endorse or accept liability for sites controlled by third-parties.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Astellas Pharma Ltd. on 0800 783 5018.