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

Evrenzo 20 mg film-coated tablets
Evrenzo 50 mg film-coated tablets
Evrenzo 70 mg film-coated tablets
Evrenzo 100 mg film-coated tablets
Evrenzo 150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Evrenzo 20 mg film-coated tablets
Each tablet contains 20 mg of roxadustat.

Evrenzo 50 mg film-coated tablets
Each tablet contains 50 mg of roxadustat.

Evrenzo 70 mg film-coated tablets
Each tablet contains 70 mg of roxadustat.

Evrenzo 100 mg film-coated tablets
Each tablet contains 100 mg of roxadustat.

Evrenzo 150 mg film-coated tablets
Each tablet contains 150 mg of roxadustat.

Excipient(s) with known effect
Each 20 mg film-coated tablet contains 40.5 mg of lactose, 0.9 mg of Allura Red AC aluminium lake and 0.21 mg soya lecithin.
Each 50 mg film-coated tablet contains 101.2 mg of lactose, 1.7 mg of Allura Red AC aluminium lake and 0.39 mg soya lecithin.
Each 70 mg film-coated tablet contains 141.6 mg of lactose, 2.1 mg of Allura Red AC aluminium lake and 0.47 mg soya lecithin.
Each 100 mg film-coated tablet contains 202.4 mg of lactose, 2.8 mg of Allura Red AC aluminium lake and 0.63 mg soya lecithin.
Each 150 mg film-coated tablet contains 303.5 mg of lactose, 3.7 mg of Allura Red AC aluminium lake and 0.84 mg soya lecithin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets (tablets).

Evrenzo 20 mg tablets
Red, oval tablets (approximately 8 mm × 4 mm) with ‘20’ debossed on one side.

Evrenzo 50 mg tablets
Red, oval tablets (approximately 11 mm × 6 mm) with ‘50’ debossed on one side.

Evrenzo 70 mg tablets
Red, round tablets (approximately 9 mm) with '70' debossed on one side.

Evrenzo 100 mg tablets
Red, oval tablets (approximately 14 mm × 7 mm) with '100' debossed on one side.

Evrenzo 150 mg tablets
Red, almond-shaped tablets (approximately 14 mm × 9 mm) with '150' debossed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Evrenzo is indicated for treatment of adult patients with symptomatic anaemia associated with chronic kidney disease (CKD).

4.2 Posology and method of administration

Treatment with roxadustat 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 deciding to increase the dose.

Anaemia symptoms and sequelae may vary with age, gender, and overall burden of disease; a physician's evaluation of the individual patient's clinical course and condition is necessary. In addition to the presence of symptoms of anaemia, criteria such as rate of fall of haemoglobin (Hb) concentration, prior response to iron therapy, and the risk of need of red blood cell (RBC) transfusion could be of relevance in the evaluation of the individual patient's clinical course and condition.

Posology
The appropriate dose of roxadustat must be taken orally three times per week and not on consecutive days.

The dose should be individualised to achieve and maintain target Hb levels of 10 to 12 g/dL as described below.

Roxadustat treatment should not be continued beyond 24 weeks of therapy if a clinically meaningful increase in Hb levels is not achieved. Alternative explanations for an inadequate response should be sought and treated before re-starting Evrenzo.

Starting dose at treatment initiation
Adequate iron stores should be ensured prior to initiating treatment.

Patients not currently treated with an erythropoiesis-stimulating agent (ESA)
For patients initiating anaemia treatment not previously treated with ESA the recommended starting dose of roxadustat is 70 mg three times per week in patients weighing less than 100 kg and 100 mg three times per week in patients weighing 100 kg and over.

Patients converting from an ESA
Patients currently treated with an ESA can be converted to roxadustat, however, conversion of dialysis patients otherwise stable on ESA treatment is only to be considered when there is a valid clinical reason (see sections 4.4 and 5.1).

Conversion of non-dialysis patients otherwise stable on ESA treatment has not been investigated. A decision to treat these patients with roxadustat should be based on a benefit-risk consideration for the individual patient.

The recommended starting dose of roxadustat is based on the average prescribed ESA dose in the 4 weeks before conversion (see Table 1). The first roxadustat dose should replace the next scheduled dose of the current ESA.

Table 1. Starting doses of roxadustat to be taken three times per week in patients converting from an ESA

Darbepoetin alfa intravenous or subcutaneous dose (micrograms/week)	**Epoetin intravenous or subcutaneous dose (IU/week)**	**Methoxy polyethylene glycol-epoetin beta intravenous or subcutaneous dose (micrograms/monthly)**	**Roxadustat dose (milligrams three times per week)**
Less than 25	Less than 5 000	Less than 80	70
25 to less than 40	5 000 up to 8 000	80 up to and including 120	100
40 up to and including 80	More than 8 000 up to and including 16 000	More than 120 up to and including 200	150
More than 80	More than 16 000	More than 200	200

ESA: erythropoiesis-stimulating agent

Dose adjustment and Hb monitoring
The individualised maintenance dose ranges from 20 mg to 400 mg three times per week (see section *maximum recommended dose*). Hb levels should be monitored every two weeks until the desired Hb level of 10 to 12 g/dL is achieved and stabilised, and every 4 weeks thereafter, or as clinically indicated.

The dose of roxadustat can be adjusted stepwise up or down from the starting dose 4 weeks after treatment start, and every 4 weeks thereafter except if the Hb increases by more than 2 g/dL, in which case the dose should be reduced by one step immediately. When adjusting the dose of roxadustat, 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 according to the dose adjustment algorithm described in Table 2.

The stepwise dose adjustments up or down should follow the sequence of the available doses:
20 mg-40 mg-50 mg-70 mg-100 mg-150 mg-200 mg-250 mg-300 mg-400 mg (only for CKD patients on dialysis).

Table 2. Dose adjustment rules

Change in Hb over the previous 4 weeks[1]	**Current Hb level (g/dL):**			
	Lower than 10.5	**10.5 to 11.9**	**12.0 to 12.9**	**13.0 or higher**
Change in value of more than +1.0 g/dL	No change	Reduce dose by one step	Reduce dose by one step	Withhold dosing, monitor Hb level and resume dosing when Hb is less than 12.0 g/dL, at a dose that is reduced by two steps
Change in value between -1.0 and +1.0 g/dL	Increase dose by one step	No change	Reduce dose by one step	
Change in value of less than -1.0 g/dL	Increase dose by one step	Increase dose by one step	No change	

The dose of roxadustat should not be adjusted more frequently than once every 4 weeks, except if Hb increases by more than 2 g/dL at any time within a 4-week period, in which case the dose should be reduced by one step immediately.
[1]Change in haemoglobin (Hb) over the previous 4 weeks = (present Hb value) – (previous Hb value drawn 4 weeks ago).

If additional dose reduction is required for a patient already on the lowest dose (20 mg three times per week), do not reduce the 20 mg dose by breaking the tablet, but reduce the dose frequency to twice per week. If further dose reduction is needed, the dose frequency may be further reduced to once weekly.

Maintenance dose
After stabilisation to target Hb levels between 10 to 12 g/dL, the Hb levels should continue to be monitored regularly and the dose adjustment rules followed (see Table 2).

Patients starting dialysis while on roxadustat treatment
No specific dose adjustment is required for CKD patients who start dialysis while on treatment with roxadustat. Normal dose adjustment rules (see Table 2) should be followed.

Concomitant roxadustat treatment with inducers or inhibitors
When initiating or discontinuing concomitant treatment with strong inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin) of CYP2C8, or inhibitors (e.g. probenecid) of UGT1A9: the Hb levels should be monitored routinely and the dose adjustment rules followed (see Table 2; see also sections 4.5 and 5.2).

Maximum recommended dose
Patients not on dialysis do not exceed a roxadustat dose of 3 mg/kg body weight or 300 mg three times per week, whichever is lower.

Patients on dialysis do not exceed a roxadustat dose of 3 mg/kg body weight or 400 mg three times per week, whichever is lower.

Missed dose
If a dose is missed, and there is more than 1 day until the next scheduled dose, the missed dose must be taken as soon as possible. If one day or less remains before the next scheduled dose, the missed dose must be skipped, and the next dose must be taken on the next scheduled day. In each case, the regular dosing schedule should be resumed thereafter.

Special populations
Elderly
No adjustment of the starting dose is required in elderly patients (see section 5.2).

Patients with hepatic impairment
No adjustment of the starting dose level is required in patients with mild hepatic impairment (Child-Pugh class A) (see sections 4.4 and 5.2).

Caution is recommended when prescribing roxadustat to patients with moderate hepatic impairment. The starting dose is to be reduced by half or to the dose level that is closest to half the starting dose when initiating treatment in 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) as the safety and efficacy has not been evaluated in this population (see sections 4.4 and 5.2).

Paediatric population
Safety and efficacy of roxadustat in paediatric patients under 18 years of age have not been established. No data are available.

Method of administration
Evrenzo film-coated tablets are to be taken orally with or without food. Tablets are to be swallowed whole and not chewed, broken or crushed due to the absence of clinical data under these conditions, and to protect the light-sensitive tablet core from photodegradation.

The tablets should be taken at least 1 hour after administration of phosphate binders (except lanthanum) or other medicinal products containing multivalent cations such as calcium, iron, magnesium or aluminium (see sections 4.5 and 5.2).

4.3 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.
- Third trimester of pregnancy (see sections 4.4 and 4.6).
- Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

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 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 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 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 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) including deep vein thrombosis (DVT), pulmonary embolism (PE) and cerebral infarction should be carefully weighed against the benefits of roxadustat treatment particularly in patients with pre-existing risk factors for TVE, including obesity and prior history of TVEs. The majority of DVT, PE and cerebral infarction events were serious. Fatal cases of cerebral infarction have been reported.

A rapid increase in Hb values has been observed in some cases of cerebrovascular accidents.

Vascular access thrombosis (VAT) was reported as very common amongst the CKD patients on dialysis in clinical studies (see section 4.8). In these patients, rates of VAT in roxadustat-treated patients were highest in the first 12 weeks following initiation of treatment, particularly at Hb values more than 12 g/dL and with Hb rise of more than 2 g/dL over 4 weeks. It is recommended to closely monitor Hb levels and adjust the dose using the dose adjustment rules (see Table 2) to avoid these levels.

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 an individual benefit-risk assessment.

Seizures

Seizures were reported as common amongst the patients in clinical studies receiving roxadustat (see 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.

Secondary hypothyroidism
Cases of secondary hypothyroidism have been reported with the use of roxadustat (see section 4.8). These reactions were reversible upon roxadustat withdrawal. Monitoring of thyroid function is recommended as clinically indicated.

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 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 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 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.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on roxadustat
Phosphate binders and other products containing multivalent cations
Co-administration of roxadustat with phosphate binders sevelamer carbonate or calcium acetate in healthy subjects decreased roxadustat AUC by 67% and 46% and C_{max} by 66% and 52%, respectively. Roxadustat may form a chelate with multivalent cations such as in phosphate binders or other products containing calcium, iron, magnesium or aluminium. Staggered administration of phosphate binders (at

least 1 hour apart) had no clinically significant effect on roxadustat exposure in patients with CKD. Roxadustat should be taken at least 1 hour after administration of phosphate binders or other medicinal products or supplements containing multivalent cations (see section 4.2). This restriction does not apply to lanthanum carbonate, as the co-administration of roxadustat with lanthanum carbonate did not result in a clinically meaningful change in the plasma exposure of roxadustat.

Modifiers of CYP2C8 or UGT1A9 activity
Roxadustat is a substrate of CYP2C8 and UGT1A9. Co-administration of roxadustat with gemfibrozil (CYP2C8 and OATP1B1inhibitor) or probenecid (UGT and OAT1/OAT3 inhibitor) in healthy subjects increased roxadustat AUC by 2.3-fold and C_{max} by 1.4-fold. Monitor Hb levels when initiating or discontinuing concomitant treatment with gemfibrozil, probenecid, other strong inhibitors or inducers of CYP2C8 or other strong inhibitors of UGT1A9. Adjust the dose of roxadustat following dose adjustment rules (see Table 2) based on Hb monitoring.

Effects of roxadustat on other medicinal products
OATP1B1 or BCRP Substrates
Roxadustat is an inhibitor of BCRP and OATP1B1. These transporters play an important role in the intestinal and hepatic uptake and efflux of statins. Co-administration of 200 mg of roxadustat with simvastatin in healthy subjects increased the AUC and C_{max} of simvastatin 1.8- and 1.9-fold, respectively, and the AUC and C_{max} of simvastatin acid (the active metabolite of simvastatin) 1.9- and 2.8-fold, respectively. 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 200 mg of roxadustat with rosuvastatin increased the AUC and C_{max} of rosuvastatin 2.9- and 4.5-fold, respectively. Co-administration of 200 mg of roxadustat with atorvastatin increased the AUC and C_{max} of atorvastatin 2.0- and 1.3-fold, respectively.

Interactions are also expected with other statins. When co-administered with roxadustat, consider this interaction, monitor for adverse reactions associated with statins and for the need of statin dose reduction. Refer to statin prescribing information when deciding on the appropriate statin dose for individual patients.

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.

Roxadustat and ESAs
It is not recommended to combine administration of roxadustat and ESAs as the combination has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy, women of childbearing potential and contraception
There are no data on the use of roxadustat in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Roxadustat is contraindicated during the third trimester of pregnancy (see sections 4.3 and 4.4).

Roxadustat is not recommended during the first and second trimester of pregnancy (see section 4.4). If pregnancy occurs while Evrenzo is being administered, treatment should be discontinued and switched to alternative treatments, if appropriate (see section 4.3).

Breast-feeding
It is unknown whether roxadustat/metabolites are excreted in human milk. Available animal data have shown excretion of roxadustat in milk (for details see section 5.3). Evrenzo is contraindicated during breast-feeding (see sections 4.3 and 5.3).

Fertility
In animal studies, there were no effects of roxadustat on male and female fertility. However, changes in rat male reproductive organs were observed. The potential effects of roxadustat on male fertility in humans is currently unknown. At a maternally toxic dose, increased embryonic loss was observed (see section 5.3). Women of childbearing potential must use highly effective contraception during treatment and for at least one week after the last dose of Evrenzo.

4.7 Effects on ability to drive and use machines

Roxadustat has minor influence on the ability to drive and use machines. Seizures have been reported during treatment with Evrenzo (see section 4.4). Therefore, caution should be exercised when driving or using machines.

4.8 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%).

Tabulated list of adverse reactions
Adverse reactions observed during clinical studies and/or in post-marketing experience are listed in this section by frequency category.
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).

Table 3. Adverse reactions

MedDRA System organ class (SOC)	**Frequency category**	**Adverse reaction**
Infections and infestations	Common	Sepsis
Blood and lymphatic system disorders	Common	Thrombocytopenia
Endocrine disorders	Not known	Secondary hypothyroidism
Metabolism and nutrition disorders	Very common	Hyperkalaemia
Psychiatric disorders	Common	Insomnia
Nervous system disorders	Common	Seizures, headache
	Uncommon	Cerebral infarction
Vascular disorders	Very common	Hypertension, vascular access thrombosis (VAT)[1]
	Common	Deep vein thrombosis (DVT)
Respiratory, thoracic, mediastinal disorders	Uncommon	Pulmonary embolism
Gastrointestinal disorders	Very common	Nausea, diarrhoea
	Common	Constipation, vomiting

MedDRA System organ class (SOC)	Frequency category	Adverse reaction
Hepatobiliary disorders	Uncommon	Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	Not known	Dermatitis Exfoliative Generalised (DEG)
General disorders and administration site conditions	Very common	Peripheral oedema
Investigations	Not known	Blood thyroid stimulating hormone (TSH) decreased, blood copper increased

[1]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 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 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 section 4.4).

In CKD patients not on dialysis, the overall incidence of Ischaemic central nervous system vascular conditions events was higher in the roxadustat group (3.9%) as compared to the placebo group (2.4%) and the follow-up adjusted incidence rate was higher in the roxadustat group (2.3) as compared to placebo group (1.8). Cerebral infarction demonstrated a 0.2% higher occurrence in the roxadustat group compared to placebo (0.6% vs 0.4%).

In CKD patients on dialysis, the overall incidence of events from Ischaemic central nervous system vascular conditions events was similar in the roxadustat treatment group (4.8%) as compared to the active control group (4.2%). The incident rate/100 patient exposure years (PEY) was 2.8 in the roxadustat treatment group as compared to 2.2 in the active control group. Ischemic stroke demonstrated a 0.2% higher occurrence in the roxadustat group compared to active comparator (0.8% vs 0.6%).

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 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 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 section 4.4).

Skin reactions
Dermatitis exfoliative generalised, part of severe cutaneous adverse reactions (SCARs), has been reported during postmarketing surveillance and has shown an association with roxadustat treatment (frequency not known).

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

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 these findings were non-serious. Roxadustat overdose can elevate Hb levels above the desired level (10 - 12 g/dL), which should be managed with discontinuation or reduction of roxadustat dosage (see section 4.2) and careful monitoring and treatment as clinically indicated. Roxadustat and its metabolites are not significantly removed by haemodialysis (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-anaemic preparations, other anti-anaemic preparations, ATC code: B03XA05.

Mechanism of action

Roxadustat is a hypoxia-inducible factor, prolyl hydroxylase inhibitor (HIF-PHI). The activity of HIF-PH enzymes controls intracellular levels of HIF, a transcription factor that regulates the expression of genes involved in erythropoiesis. Activation of the HIF pathway is important in the adaptative response to hypoxia to increase red blood cell production. Through the reversible inhibition of HIF-PH, roxadustat stimulates a coordinated erythropoietic response that includes the increase of plasma endogenous erythropoietin (EPO) levels, regulation of iron transporter proteins and reduction of hepcidin (an iron regulator protein that is increased during inflammation in CKD). This results in improved iron bioavailability, increased Hb production and increased red cell mass.

Pharmacodynamic effects
Effects on QTc and heart rate
A thorough QT (TQT) study in healthy subjects with roxadustat at a single therapeutic dose of 2.75 mg/kg and a single supratherapeutic dose of 5 mg/kg (up to 510 mg) did not show a prolongation of the QTc interval. The same thorough QT study demonstrated a placebo-corrected heart rate increase of up to 9 to 10 bpm at 8 to 12 h post-dose for the 2.75 mg/kg dose and 15 to 18 bpm at 6 to 12 h post-dose for the dose of 5 mg/kg.

Clinical efficacy and safety

Development program in anaemia with CKD

Efficacy and safety of roxadustat were evaluated for at least 52 weeks in a globally conducted phase 3 program comprising of 8 multicentre and randomized studies in non-dialysis dependent (NDD) and dialysis-dependent (DD) CKD patients with anaemia (see Table 4).

Three studies in stage 3-5 CKD NDD patients were double-blind and placebo-controlled studies (ALPS, 1517-CL-0608; ANDES, FGCL-4592-060; OLYMPUS, D5740C00001) and one study was open-label ESA-controlled (DOLOMITES, 1517-CL-0610) using darbepoetin alfa as comparator. All NDD studies assessed efficacy and safety in ESA-untreated patients by correcting and thereafter maintaining Hb in the target range of 10 to 12 g/dL (Hb correction setting).

Four open-label ESA-controlled DD studies (control: epoetin alfa and/or darbepoetin alfa) in patients on haemodialysis or peritoneal dialysis assessed the efficacy and safety in different settings:

- in a Hb correction setting (HIMALAYAS, FGCL-4592-063).
- in an ESA conversion setting converting patients from treatment with an ESA to maintain Hb in the target range (PYRENEES, 1517-CL-0613; SIERRAS, FGCL-4592-064).
- or combining the Hb correction and ESA conversion approaches (ROCKIES, D5740C00002).

Patients in the NDD studies had CKD stage 3 to 5 and were not receiving dialysis. All patients had an average Hb ≤10.0 g/dL except patients in the DOLOMITES study (1517-CL-0610), which allowed an average Hb ≤10.5 g/dL. Ferritin levels were required to be ≥30 ng/mL (ALPS, 1517-CL-0608; ANDES, FGCL-4592-060), ≥50 ng/mL (OLYMPUS, D5740C00001) or ≥100 ng/mL (DOLOMITES, 1517-CL-0610). Except for those in the (OLYMPUS, D5740C00001) study, which allowed ESA treatment until 6 weeks prior to randomization, patients could not have received any ESA treatment within 12 weeks of randomization.

Patients in the DD studies had to be on dialysis: stable DD for patients in the PYRENEES study (1517-CL-0613), which was defined as dialysis for longer than 4 months; or incident (ID), DD for patients in the HIMALAYAS study (FGCL-4592-063), which was defined as dialysis ≥2 weeks but ≤4 months. Patients in the SIERRAS (FGCL-4592-064) and ROCKIES studies (D5740C00002) included both stable (approximately 80% to 90%) and ID (approximately 10% to 20%) DD patients. Ferritin was required to be ≥100 ng/mL in all patients. All patients required intravenous or subcutaneous ESA for at least 8 weeks prior to randomization, except those patients in the HIMALAYAS study (FGCL-4592-063) which excluded patients who had received any ESA treatment within 12 weeks prior to randomization.

Treatment with roxadustat followed the principles of dosing instructions as described in section 4.2. Demographics and all baseline characteristics across individual studies were comparable between the roxadustat and control groups. The median age at randomization was 55 to 69 years, with between 16.6% and 31.1% in the 65-74 age range, and between 6.8% and 35% who were ≥75 years of age. The percentage of female patients ranged from 40.5% to 60.7%. The most commonly represented races across the studies were White, Black or African American and Asian. The most common CKD aetiologies were diabetic and hypertensive nephropathy. Median Hb levels ranged from 8.60 to 10.78 g/dL. Approximately 50-60% of NDD patients and 80-90% of DD patients were iron replete at baseline.

Data from seven phase 3 studies were pooled in two separate populations (three NDD and four DD) (see Table 4).

Three placebo-controlled NDD Studies (2,386 patients on roxadustat; 1,884 patients on placebo) were included in the NDD pool. Data from the phase 3 ESA-controlled NDD DOLOMITES study (1517-CL-0610; 323 patients on roxadustat and 293 patients on darbepoetin alfa) are not included in the NDD pooled analyses as this study is the only open-label, active-controlled study in the NDD population.

Four ESA-controlled DD Studies (2,354 patients on roxadustat; 2,360 patients on ESA [epoetin alfa and/or darbepoetin alfa]) were included in the DD pool. Within the DD pool, two sub pools were established to reflect the two different treatment settings:

- Patients in the DD population who were on dialysis for greater than 2 weeks and less than 4 months were termed incident (ID) DD patients (ID DD pool) reflective of the Hb correction setting.
- The DD patients who were on dialysis after this threshold of four months were termed stable DD patients (Stable DD pool) reflective of the ESA conversion setting.

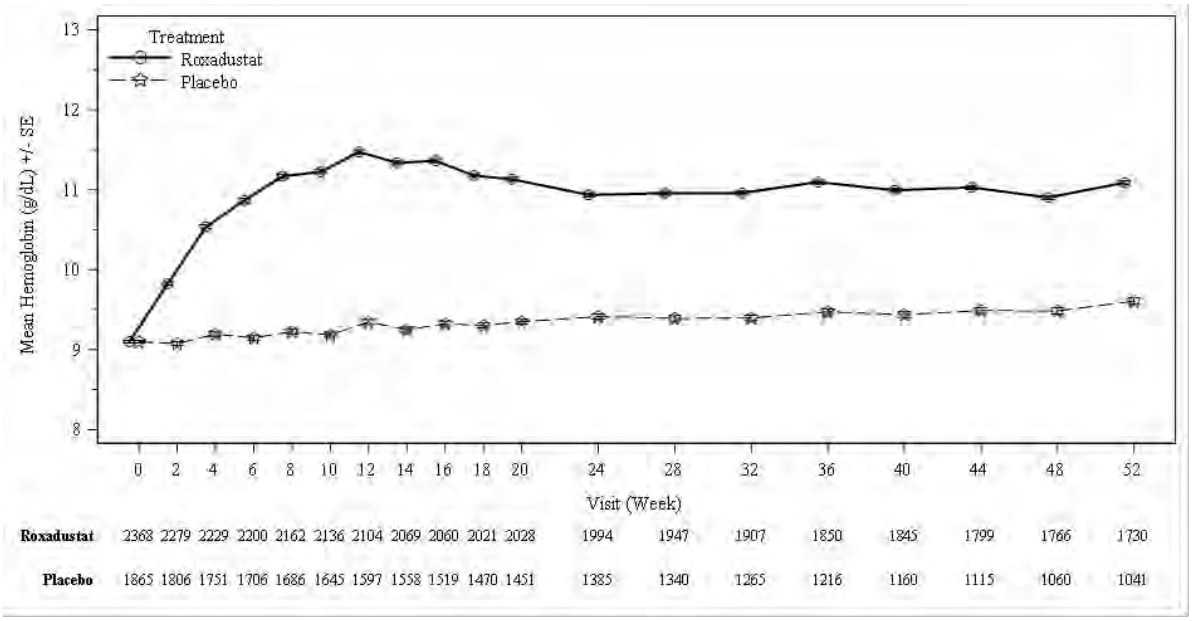
Table 4. Overview on Roxadustat phase 3 development program in anaemia with CKD

Studies in NDD patients				
	Placebo-controlled studies (NDD pool)			**ESA-control (Darbepoetin alfa)**
Setting	Hb correction			
Study	ALPS (1517-CL-0608)	ANDES (FGCL-4592-060)	OLYMPUS (D5740C00001)	DOLOMITES (1517-CL-0610)
Randomized (roxadustat/ comparator)	594 (391/203)	916 (611/305)	2760 (1384/1376)	616 (323/293)
Studies in DD patients				
	ESA-controlled studies (DD pool) (Epoetin alfa or Darbepoetin alfa)			
Setting	ESA conversion		Hb correction	ESA conversion and Hb correction
Study	PYRENEES (1517-CL-0613)	SIERRAS (FGCL-4592-064)	HIMALAYAS (FGCL-4592-063)	ROCKIES (D5740C00002)
Randomized (roxadustat/ comparator)	834 (414/420)	740 (370/370)	1039 (522/517)	2101 (1048/1053)

DD: dialysis dependent; ESA: erythropoiesis-stimulating agent; Hb: haemoglobin; NDD: non-dialysis dependent.

NDD CKD patients
Efficacy results
Course of Hb during treatment
In clinical studies, roxadustat was effective in achieving and maintaining target Hb levels (10-12 g/dL) in patients with CKD anaemia not on dialysis (see Figure 1).

Figure 1. Mean (SE) Hb (g/dL) over time up to week 52 (FAS); NDD pool (Hb correction)



FAS: full analysis set; Hb: haemoglobin; NDD: non-dialysis dependent; SE: standard error.

Key Hb efficacy endpoints in NDD CKD patients
In NDD patients in need of anaemia treatment for Hb correction, the proportion of patients who achieved Hb response during the first 24 weeks was higher in the roxadustat group (80.2%) compared with placebo (8.7%). There was a statistically significant increase in Hb from baseline to weeks 28 to 36 in the roxadustat group (1.91 g/dL) compared with placebo (0.14 g/dL) and the lower limit of the 95% confidence interval is above 1. In the NDD studies, an increase in Hb of at least 1 g/dL was achieved with a median time of 4.1 weeks (see Table 5).

In the open-label ESA-controlled NDD DOLOMITES (1517-CL-0610) study, the proportion of patients who achieved Hb response during the first 24 weeks was non-inferior in the roxadustat group (89.5%) compared with darbepoetin alfa (78%) (see Table 5).

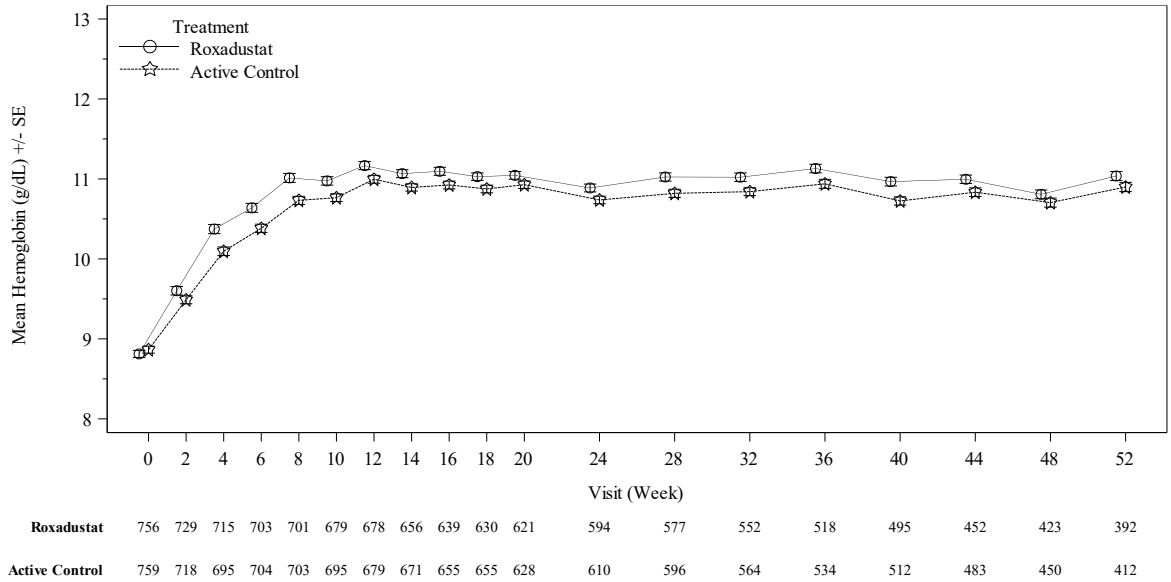
Table 5. Key Hb efficacy endpoints (NDD)

Population	**NDD CKD patients**			
Setting	**Hb correction**		**Hb correction**	
	NDD pool (FAS)		**DOLOMITES (PPS)** 1517-CL-0610	
Endpoint/Parameter	**Roxadustat n = 2368**	**Placebo n = 1865**	**Roxadustat n = 286**	**Darbepoetin alfa n = 273**
Proportion of patients who achieved Hb response[1]				
Responders, n (%) [95% CI]	1,899 (80.2) [78.5, 81.8]	163 (8.7) [7.5, 10.1]	256 (89.5) [85.4, 92.8]	213 (78.0) [72.6, 82.8]
Difference of proportions [95% CI]	71.5 [69.40, 73.51]		11.51 [5.66, 17.36]	
Odds ratio [95% CI]	40.49 [33.01, 49.67]		2.48 [1.53, 4.04]	
P value	< 0.0001		ND	
Change from baseline in Hb (g/dL)[2]				
Mean (SD) baseline	9.10 (0.74)	9.10 (0.73)	9.55 (0.76)	9.54 (0.69)
Mean (SD) CFB	1.85 (1.07)	0.17 (1.08)	1.85 (1.08)	1.84 (0.97)
LS mean	1.91	0.14	1.85	1.84
LS mean difference [95% CI]	1.77 [1.69, 1.84]		0.02 [-0.13, 0.16]	
P value	< 0.0001		0.844	

CFB: change from baseline; CI: confidence interval; CKD: chronic kidney disease; FAS: full analysis set; Hb: haemoglobin; LS: Least squares; ND: not done; NDD: non-dialysis dependent; PPS: per protocol set; SD: standard deviation.
[1]Hb response within the first 24 weeks.
[2]Change from baseline in Hb to Weeks 28 to 36.

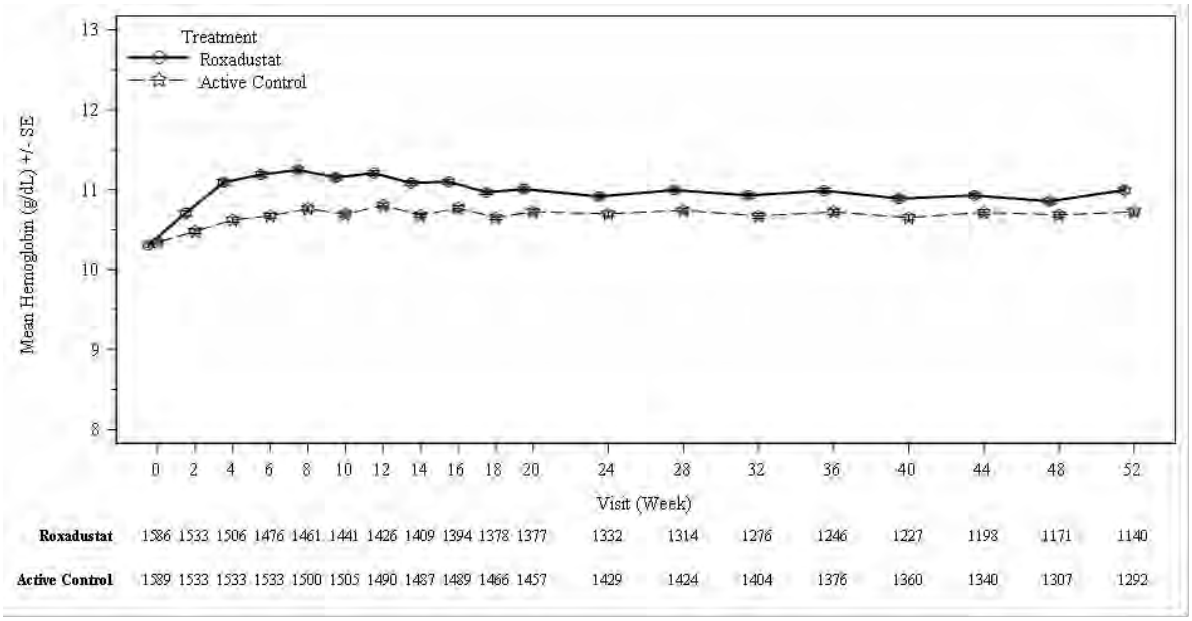
DD CKD patients
Course of Hb during treatment
In clinical studies, roxadustat was effective in achieving and maintaining target Hb levels (10-12 g/dL) in CKD patients on dialysis, irrespective of prior ESA treatment (see Figures 2 and 3).

Figure 2. Mean (SE) Hb up to week 52 (FAS); ID DD subpool (Hb correction)



DD: dialysis-dependent; FAS: full analysis set; Hb: haemoglobin; ID: incident; SE: standard error.

Figure 3. Mean (SE) Hb (g/dL) over time up to week 52 (FAS); stable DD subpool (ESA conversion)



DD: dialysis dependent; ESA: erythropoiesis-stimulating agent; FAS: full analysis set; Hb: haemoglobin; SE: standard error.

Key Hb efficacy endpoints in DD CKD patients
In DD patients in need of anaemia treatment for Hb correction and those converted from ESA treatment, there was an increase in Hb from baseline to weeks 28 to 36 in the roxadustat group; this increase was comparable to that observed in the ESA group and was above the prespecified noninferiority margin of -0.75 g/dL. The proportion of patients who achieved Hb response during the first 24 weeks was similar in the roxadustat and ESA groups (see Table 6).

Table 6. Key Hb efficacy endpoints (DD)

Population	**DD Patients**			
Setting	**Hb Correction**		**ESA Conversion**	
	ID DD pool (FAS/PPS)		**Stable DD Pool (PPS)**	
Endpoint/Parameter	**Roxadustat n = 756**	**ESA n = 759**	**Roxadustat n = 1379**	**ESA n = 1417**
Change from baseline in Hb (g/dL)				
Mean (SD) baseline	8.77 (1.20)	8.82 (1.20)	10.32 (0.99)	10.37 (0.99)
Mean (SD) CFB	2.37 (1.57)	2.12 (1.46)	0.65 (1.15)	0.36 (1.23)
LS mean	2.17	1.89	0.58	0.28
LS mean difference [95% CI]	0.28 [0.110, 0.451]		0.30 [0.228, 0.373]	
P value	0.0013		< 0.0001	
Proportion of patients who achieved Hb response[1,2]				
Responders, n (%) [95% CI]	453 (59.9) [56.3, 63.4]	452 (59.6) [56.0, 63.1]	978 (70.9) [68.4, 73.3]	959 (67.7) [65.2, 70.1]
Difference of proportions [95% CI]	0.3 [-4.5, 5.1]		2.7 [-0.7, 6.0]	
Odds ratio [95% CI]	ND		ND	
P value	ND		ND	

CFB: change from baseline; CI: confidence interval; CKD: chronic kidney disease; DD: dialysis dependent; ESA: erythropoiesis-stimulating agent; FAS: full analysis set; Hb: haemoglobin; ID: incident; LS: Least squares; ND: not done; PPS: per protocol set; SD: standard deviation.
[1]Hb within the target range of 10.0 to 12.0 g/dL during weeks 28 to 36 without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period.
[2]Data in the ID DD pool were only analysed for weeks 28 to 52.

Rescue therapy, RBC transfusion and intravenous iron
The effects of treatment with roxadustat on use of rescue therapy, RBC transfusion and intravenous iron are presented in Table 7 (NDD) and Table 8 (DD). In clinical studies, roxadustat reduced hepcidin (regulator of iron metabolism), reduced ferritin, increased serum iron while transferrin saturation was stable, all which were assessed over time as indicators of iron status.

Low-density lipoprotein (LDL) cholesterol
The effects of treatment with roxadustat on LDL cholesterol are presented in Tables 7 and 8. There was a reduction in mean LDL and high density lipoprotein (HDL) cholesterol levels in roxadustat-treated patients compared with placebo or ESA-treated patients. The effect on LDL cholesterol was more pronounced, leading to a reduction of the LDL/HDL ratio and was observed regardless of the use of statins.

Table 7. Other efficacy endpoints: use of rescue therapy, monthly intravenous iron use and change from baseline in LDL cholesterol (NDD)

Population	**NDD CKD patients**			
Intervention	**Correction**		**Correction**	
	NDD pool (FAS)		**DOLOMITES (1517-CL-0610)**	
Endpoint/Parameter	**Roxadustat n = 2368**	**Placebo n = 1865**	**Roxadustat n = 322**	**Darbepoetin alfa n = 292**
Number of patients with rescue therapy, n (%)[1]	211 (8.9)	580 (31.1)	ND	
RBC	118 (5.0)	240 (12.9)		
IV iron	50 (2.1)	90 (4.8)		
ESA	48 (2.0)	257 (13.8)		
IR	10.4	41.0		
Hazard ratio	0.19		ND	
95% CI	0.16, 0.23			
P value	< 0.0001			
Number of Patients with IV Iron, n (%)[2]	ND		20 (6.2)	37 (12.7)
IR			9.9	21.2
Hazard ratio			0.45	
95% CI			0.26, 0.78	
P value			0.004	
Change from baseline in LDL cholesterol (mmol/L) to weeks 12 to 28[3]				
Analysis using ANCOVA				
LS mean	-0.446	0.066	-0.356	0.047
95% CI	-0.484, -0.409	0.017, 0.116	-0.432, -0.280	-0.033, 0.127
LS mean difference (R-comparator)	-0.513		-0.403	
95% CI	-0.573, -0.453		-0.510, -0.296	
P value	< 0.0001		< 0.001	

P values presented for the NDD pool are nominal p values.
ANCOVA: analysis of covariance; CI: confidence interval; ESA: erythropoiesis-stimulating agent; FAS: full analysis set; IR: incidence rate (per 100 patient-years at risk); IV: intravenous; LDL: low density lipoprotein; LS: least squares; ND: not done; NDD: non-dialysis-dependent; R: roxadustat; RBC: red blood cell;
[1]For use of rescue therapy the NDD pool was analysed up to week 52.
[2]During weeks 1-36.
[3]Change from baseline in LDL cholesterol was assessed only through week 24 for study OLYMPUS (D5740C00001).

Table 8. Other efficacy endpoints: use of rescue therapy, monthly intravenous iron use and change from baseline in LDL cholesterol (DD)

Population	**DD CKD patients**			
Intervention	**Correction**		**Conversion**	
	ID DD pool (FAS)		**Stable DD pool (FAS)**	
Endpoint/ Parameter	**Roxadustat n = 756**	**ESA n = 759**	**Roxadustat n = 1586**	**ESA n = 1589**
Mean monthly IV iron over weeks 28 - 52 (mg)[1]				
n	606	621	1414	1486
Mean (SD)	53.57 (143.097)	70.22 (173.33)	42.45 (229.80)	61.99 (148.02)
Change from baseline in LDL cholesterol (mmol/L) to weeks 12 to 28				
Analysis using ANCOVA				
LS mean	-0.610	-0.157	-0.408	-0.035
95% CI	-0.700, -0.520	-0.245, -0.069	-0.449, -0.368	-0.074, 0.003
LS mean difference (R-comparator)	-0.453		-0.373	
95% CI	-0.575, -0.331		-0.418, -0.328	
P value	< 0.0001		< 0.0001	

P values presented for the ID DD and stable DD pools are nominal p values.
ANCOVA: analysis of covariance; CI: confidence interval; CKD: chronic kidney disease; DD: dialysis-dependent; ESA: erythropoiesis-stimulating agent; FAS: full analysis set; ID: incident dialysis; IV: intravenous; LDL: low density lipoprotein; LS: least squares; R: roxadustat.
[1]Time period for PYRENEES (1517-CL-0613) study was up to week 36, and the time period for ROCKIES (D5740C0002) study was from week 36 through end of study.

In the dialysis study SIERRAS (FGCL-4592-064) a significantly lower proportion of patients received a red blood cell transfusion during treatment in the roxadustat group compared with the EPO-alfa group (12.5% versus 21.1%); the numerical reduction was not statistically significant in the ROCKIES (D5740C00002) study (9.8% versus 13.2%).

Patient reported outcomes not on dialysis
In the DOLOMITES study (1517-CL-0610) noninferiority of roxadustat to darbepoetin was established with regards to SF-36 PF and SF-36 VT.

Patient reported outcomes on dialysis
In the PYRENEES study (1517-CL-0613), non-inferiority of roxadustat to ESAs was established regarding SF-36 PF and SF-36 VT changes from baseline to weeks 12 to 28.

Clinical safety
Meta-analysis of pooled, adjudicated cardiovascular events
A meta-analysis, of adjudicated major adverse cardiovascular events (MACE; a composite of all-cause mortality [ACM], myocardial infarction, stroke) and MACE+ (a composite of ACM, myocardial infarction, stroke, and hospitalisation for either unstable angina or congestive heart failure), from the phase 3 study program was conducted in 8984 patients.

MACE, MACE+ and ACM outcomes are presented for three datasets using the pooled hazard ratio (HR) and its 95% confidence interval (CI). The three datasets include:

- A pooled placebo-controlled Hb correction dataset in NDD patients [includes patients from studies OLYMPUS (D5740C00001), ANDES (FGCL-4592-060) and ALPS (1517-CL-0608); see Table 4]

- A pooled ESA-controlled Hb correction dataset in NDD and ID-DD patients [includes patients from studies DOLOMITES (1517-CL-0610), HIMALAYAS (FGCL-4592-063), and the ID-DD patients of studies SIERRAS (FGCL-4592-064) and ROCKIES (D5740C00002); see Table 4]
- A pooled ESA-controlled ESA conversion dataset in Stable DD patients [includes patients from study PYRENEES (1517-CL-0613) and Stable DD patients from studies ROCKIES (D5740C00002) and SIERRAS (FGCL-4592-064); see Table 4]

MACE, MACE+ and ACM in the placebo-controlled Hb correction set of non-dialysis-dependent CKD patients

In NDD patients the analysis for MACE, MACE+ and ACM of the on-treatment analyses included all data from the start of study treatment until 28 days of the end of treatment follow-up. The on-treatment analyses used a Cox model weighted inversely for the probability of censoring (IPCW method) which aims to correct for follow-up time differences between roxadustat and placebo including identified contributors to increased risk and early discontinuation, in particular estimated glomerular filtration rate (eGFR) determinants and Hb at baseline and over time. Whether any residual confounding is present with this model remains uncertain. The HRs for the on-treatment analyses were 1.26, 1.17 and 1.16 (see Table 9). The ITT analyses included all data from the start of study treatment until the end of posttreatment safety follow-up. The ITT analysis has been included to illustrate an imbalance in risk distribution favouring placebo in the on-treatment analysis, however, ITT analyses generally demonstrate a dilution of study drug treatment effect and in these ITT analyses bias cannot be completely excluded, especially as ESA rescue therapy was introduced after study treatment discontinuation. The HRs were 1.10, 1.07 and 1.08, with upper limits of the 95% CIs of 1.27, 1.21 and 1.26, respectively.

Table 9. CV safety and mortality in placebo-controlled Hb correction NDD pool

	MACE		**MACE+**		**ACM**	
	Roxadustat n = 2386	**Placebo n = 1884**	**Roxadustat n = 2386**	**Placebo n = 1884**	**Roxadustat n = 2386**	**Placebo n = 1884**
On-treatment						
Number of patients with events (%)	344 (14.4)	166 (8.8)	448 (18.8)	242 (12.8)	260 (10.9)	122 (6.5)
FAIR	8.7	6.8	11.6	10.1	6.4	5.0
HR (95% CI)	1.26 (1.02, 1.55)		1.17 (0.99, 1.40)		1.16 (0.90, 1.50)	
ITT						
Number of patients with events (%)	480 (20.1)	350 (18.6)	578 (24.2)	432 (22.9)	400 (16.8)	301 (16)
FAIR	10.6	10.3	13.2	13.2	8.3	8.1
HR (95% CI)	1.10 (0.96, 1.27)		1.07 (0.94, 1.21)		1.08 (0.93, 1.26)	

ACM: all-cause mortality; ACM is a component of MACE/MACE+; CI: confidence interval; FAIR: follow-up adjusted incidence rate (number of patients with event/100 patient years); HR: hazard ratio; ITT: intent-to-treat; MACE: major adverse cardiovascular event (death, non-fatal myocardial infarction and/or stroke); MACE+: major adverse cardiovascular event including hospitalisations for either unstable angina and/or congestive heart failure.

MACE, MACE+ and ACM in the ESA-controlled Hb correction set of non-dialysis-dependent and incident dialysis-dependent CKD patients

In the Hb correction setting of NDD and ID-DD patients baseline characteristics and treatment discontinuation rates were comparable between the pooled roxadustat and pooled ESA patients. The analysis for MACE, MACE+ and ACM observed on treatment showed HRs of 0.79, 0.78 and 0.78, with upper limits of the 95% CIs of 1.02, 0.98 and 1.05, respectively (see Table 10). The on-treatment analyses support no evidence of increased cardiovascular safety or mortality risk with roxadustat compared with ESA in CKD patients requiring Hb correction.

Table 10. CV safety and mortality in ESA-controlled Hb correction pool

	MACE		MACE+		ACM	
	Roxadustat n = 1083	**ESA n = 1059**	**Roxadustat n = 1083**	**ESA n = 1059**	**Roxadustat n = 1083**	**ESA n = 1059**
On-treatment						
Number of patients with events (%)	105 (9.7)	136 (12.8)	134 (12.4)	171 (16.1)	74 (6.8)	99 (9.3)
IR	6.5	8.2	8.3	10.3	4.6	6.0
HR (95% CI)	0.79 (0.61, 1.02)		0.78 (0.62, 0.98)		0.78 (0.57, 1.05)	

ACM: all-cause mortality; ACM is a component of MACE/MACE+, CI: confidence interval; ESA: erythropoiesis-stimulating agent; HR: hazard ratio; IR: incidence rate (number of patients with event/100 patient years); MACE: major adverse cardiovascular event (death, non-fatal myocardial infarction and/or stroke); MACE+: major adverse cardiovascular event including hospitalisations for either unstable angina and/or congestive heart failure.

MACE, MACE+ and ACM in ESA-controlled ESA conversion set of stable dialysis-dependent CKD patients

In stable DD patients converting from ESA analysis results for MACE, MACE+ and ACM observed on treatment showed HRs of 1.18, 1.03 and 1.23, with upper limits of the 95% CIs for HRs of 1.38, 1.19 and 1.49, respectively (see Table 11). The results in Table 11 should be interpreted with caution as patients allocated to roxadustat were switched from ESA at the start of the study and the impact of an inherent risk in switching to any new treatment versus remaining on a treatment with a stabilised Hb may confound the observed results and thus any comparison of treatment effect estimates cannot be reliably established.

Table 11. CV safety and mortality in ESA-controlled ESA conversion stable DD pool

	MACE		MACE+		ACM	
	Roxadustat n = 1594	**ESA n = 1594**	**Roxadustat n = 1594**	**ESA n = 1594**	**Roxadustat n = 1594**	**ESA n = 1594**
On-treatment						
Number of patients with events (%)	297 (18.6)	301 (18.9)	357 (22.4)	403 (25.3)	212 (13.3)	207 (13.0)
IR	10.4	9.2	12.5	12.3	7.4	6.3
HR (95% CI)	1.18 (1.00, 1.38)		1.03 (0.90, 1.19)		1.23 (1.02, 1.49)	

ACM: all-cause mortality; ACM is a component of MACE/MACE+; CI: confidence interval; ESA: erythropoiesis-stimulating agent; HR: hazard ratio; IR: incidence rate (number of patients with event/100 patient years); MACE: major adverse cardiovascular event (death, non-fatal myocardial infarction and/or stroke); MACE+: major adverse cardiovascular event including hospitalisations for either unstable angina and/or congestive heart failure.

5.2 Pharmacokinetic properties

Roxadustat plasma exposure (area under the plasma drug concentration over time curve [AUC] and maximum plasma concentrations [C_{max}]) is dose-proportional within the recommended therapeutic dose range. In a three times per week dosing regimen, steady-state roxadustat plasma concentrations are achieved within one week (3 doses) with minimal accumulation. The pharmacokinetics of roxadustat do not change over time.

Absorption

Maximum plasma concentrations (C_{max}) are usually achieved at 2 hours post dose in the fasted state. Administration of roxadustat with food decreased C_{max} by 25% but did not alter AUC as compared with the fasted state. Therefore, roxadustat can be taken with or without food (see section 4.2).

Distribution
Roxadustat is highly bound to human plasma proteins (approximately 99%), predominantly to albumin. The blood-to-plasma ratio of roxadustat is 0.6. The apparent volume of distribution at steady state is 24 L.

Biotransformation
Based on *in vitro* data, roxadustat is a substrate for CYP2C8 and UGT1A9 enzymes, as well as BCRP, OATP1B1, OAT1 and OAT3. Roxadustat is not a substrate for OATP1B3 or P-gp. Roxadustat is primarily metabolised to hydroxy-roxadustat and roxadustat-*O*-glucuronide. Unchanged roxadustat was the major circulating component in human plasma; no detectable metabolite in human plasma constituted more than 10% of total drug-related material exposure and no human specific metabolites were observed.

Elimination
The mean effective half-life ($t_{1/2}$) of roxadustat is approximately 15 hours in patients with CKD.
The apparent total body clearance (CL/F) of roxadustat is 1.1 L/h in patients with CKD not on dialysis and 1.4 L/h in patients with CKD on dialysis. Roxadustat and its metabolites are not significantly removed by haemodialysis.
When radiolabelled roxadustat was administered orally in healthy subjects, the mean recovery of radioactivity was 96% (50% in faeces, 46% in urine). In faeces, 28% of the dose was excreted as unchanged roxadustat. Less than 2% of the dose was recovered in urine as unchanged roxadustat.

Special Populations
Effects of age, sex, body weight, and race
No clinically relevant differences in the pharmacokinetics of roxadustat were observed based on age (≥18), sex, race, body weight, renal function (eGFR) or dialysis status in adult patients with anaemia due to CKD.

Haemodialysis
In dialysis-dependent CKD patients, no marked differences in pharmacokinetic parameter values were observed when roxadustat was administered 2 hours before or 1 hour after haemodialysis. Dialysis is a negligible route of overall clearance of roxadustat.

Hepatic impairment
Following a single dose of 100 mg roxadustat, mean roxadustat AUC was 23% higher and mean C_{max} was 16% lower in subjects with moderate hepatic impairment (Child-Pugh Class B) and normal renal function compared to subjects with normal hepatic and renal functions. Subjects with moderate hepatic impairment (Child-Pugh Class B) and normal renal function showed an increase in unbound roxadustat AUC_{inf} (+70%) as compared to healthy subjects.
The pharmacokinetics of roxadustat in subjects with severe hepatic impairment (Child-Pugh Class C) have not been studied.

Drug-Drug Interactions
Based on *in vitro* data, roxadustat is an inhibitor of CYP2C8, BCRP, OATP1B1 and OAT3 (see section 4.5). The pharmacokinetics of rosiglitazone (moderate sensitive CYP2C8 substrate) were not affected by co-administration of roxadustat. Roxadustat may be an inhibitor of intestinal but not hepatic UGT1A1 and showed no inhibition of other CYP metabolising enzymes or transporters, or induction of CYP enzymes at clinically relevant concentrations. There is no clinically significant effect of oral adsorptive charcoal or omeprazole on roxadustat pharmacokinetics. Clopidogrel has no effect on roxadustat exposure in patients with CKD.

5.3 Preclinical safety data

Repeat-dose toxicity studies
In the 26-week intermittent repeat dose study in Sprague-Dawley or Fisher rats, roxadustat at approximately 4 to 6-fold the total AUC at Maximum Recommended Human Dose (MRHD) resulted in histopathological findings including aortic and atrioventricular valves (A-V) valvulopathies. These

findings were present in surviving animals at the time of termination as well as in animals terminated early in a moribund state. Furthermore, the findings were not fully reversible as they were also present in animals at the end of a 30-day recovery period.

Exaggerated pharmacology resulting in excessive erythropoiesis has been observed in repeated-dose toxicity studies in healthy animals.

Haematological changes such as decreases in circulating platelets as well as increases in activated partial thromboplastin time and prothrombin time were noted in rats from approximately 2-fold the total AUC at MRHD. Thrombi were noted in the bone marrow (systemic exposures of approximately 7-fold the total AUC at MRHD in rats), kidneys (systemic exposures of approximately 5 to 6-fold total AUC at MRHD in rats), lungs (systemic exposures approximately 8- and 2-fold total AUC at MRHD in rats and cynomolgus monkeys, respectively), and the heart (systemic exposures of approximately 4 to 6-fold the total AUC at MRHD in rats).

Brain safety
In the 26-week intermittent repeat dose study in Sprague-Dawley rats, one animal, at approximately 6-fold the total AUC at MRHD showed a histologic finding of brain necrosis and gliosis. In Fisher rats, treated for the same duration, brain/hippocampal necrosis was noted in a total of four animals at the approximately 3 to 5-fold the total AUC at MRHD.

Cynomolgus monkeys intermittently administered roxadustat for 22 or 52-weeks, did not show similar findings at systemic exposures up to approximately 2-fold the total AUC at MRHD.

Carcinogenicity and mutagenicity
Roxadustat was negative in the *in vitro* Ames mutagenicity test, *in vitro* chromosome aberration test in human peripheral blood lymphocytes and an *in vivo* micronucleus test in mice at 40-fold the MRHD based on a human equivalent dose.

In the mouse and rat carcinogenicity studies, animals were administered roxadustat with the clinical dosing regimen of three times per week. Due to the rapid clearance of roxadustat in rodents, systemic exposures were not continuous throughout the dosing period. As such, possible off-target carcinogenic effects may be underestimated.

In the 2-year mouse carcinogenicity study, significant increases in the incidence of lung bronchoalveolar carcinoma was noted in the low and high dose groups (systemic exposures approximately 1-fold and approximately 3-fold the total AUC at MRHD). A significant increase in subcutis fibrosarcoma was seen in females at the high dose group (systemic exposures approximately 3-fold total AUC at MRHD).

In the 2-year rat carcinogenicity study, a significant increase in the incidence of mammary gland adenoma was noted at the middle dose level (systemic exposure less than 1-fold the total AUC at MRHD). However, the finding was not dose related and the incidence of this tumour type was lower at the highest dose level tested (systemic exposure approximately 2-fold the total AUC at MRHD) and was therefore not considered test article related.

Similar findings from the mouse and rat carcinogenicity studies were not observed in the clinical studies.

Reproductive and developmental toxicity
Roxadustat had no effect on mating or fertility in treated male or female rats at approximately 4-fold the human exposure at the MRHD. However, at the NOAEL in male rats, there were decreases in weights of the epididymis and the seminal vesicles (with fluid) without effects on male fertility. The NOEL for any male reproductive organ related findings was 1.6-fold MRHD. In female rats there were increases in the number of non-viable embryos and post-implantation losses at this dose level compared to control animals.

Results from the reproductive and developmental toxicity studies in rats and rabbits demonstrated reduction of average foetal or pup body weight, average placental weight increase, abortion and pup mortalities.

Pregnant Sprague-Dawley rats administered roxadustat daily from implantation through the closure of the hard palate (Gestation Days 7 – 17) showed decreased foetal body weight and increased skeletal alterations at approximately 6-fold the total AUC at MRHD. Roxadustat had no effect on post-implant foetal survival.

Pregnant New Zealand rabbits were administered roxadustat daily from Gestation Day 7 through Gestation Day 19 and Caesarian sections were performed on Gestation Day 29. Roxadustat administration at systemic exposures up to approximately 3-fold the total AUC at MRHD showed no embryo-foetal findings. However, one doe aborted at approximately 1-fold the total AUC at MRHD and 2 does aborted at approximately 3-fold the total AUC at MRHD, the aborting females showed thin body condition.

In the perinatal/postnatal development study in Sprague-Dawley rats, pregnant dams were administered roxadustat daily from Gestation Day 7 to Lactation Day 20. During the lactation period, pups from dams administered roxadustat at approximately 2-fold the total C_{max} at MRHD showed high mortality during the preweaning period and were sacrificed at weaning. Pups from dams administered roxadustat at doses resulting in systemic exposures approximately 3-fold the human exposure at MRHD showed a significant decrease in 21-day survival after birth (lactation index) compared with pups from control litters.

In a cross-fostering study, the most pronounced effects on rat pup viability were noted in the pups exposed to roxadustat postnatally only, and the pup viability exposed to roxadustat until delivery was lower than that of unexposed pups.

The cross-fostering study in which pups from unexposed rats were cross fostered with dams treated with roxadustat (human equivalent dose approximately 2-fold MRHD), had roxadustat in pup plasma indicating transfer of drug via the milk. Milk from these dams had roxadustat present. The pups who were exposed to milk containing roxadustat showed a lower survival rate (85.1%) versus pups from untreated dams cross fostered with untreated dams (98.5% survival rate). The mean body weight of the surviving pups exposed to roxadustat during the lactation period was also less than the control pups (no *in utero* exposure – no exposure in milk).

Cardiovascular safety
A cardiovascular safety pharmacology study showed heart rate increases following a single administration of 100 mg/kg roxadustat to monkeys. There was no effect on hERG or ECG. Additional safety pharmacology studies in rats have shown that roxadustat reduced total peripheral resistance followed by a reflex increase in heart rate from approximately six times the exposure at the MRHD.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Cellulose, microcrystalline (E460 (i))
Croscarmellose sodium (E468)
Povidone (E1201)
Magnesium stearate (E470b)

Film-coating
Poly(vinyl alcohol) (E1203)
Talc (E553b)

Macrogol (E1521)
Allura Red AC aluminium lake (E129)
Titanium dioxide (E171)
Lecithin (soya) (E322)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/aluminium perforated unit dose blisters in cartons.
Pack sizes: 12 x 1 and 36 x 1 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

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

7. MARKETING AUTHORISATION HOLDER

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

12 x 1 film-coated tablets
EU/1/21/1574/001 – 005

36 x 1 film-coated tablets
EU/1/21/1574/006 – 010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 August 2021

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) 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(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Delpharm Meppel B.V.
Hogemaat 2
7942 JG Meppel
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

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

- **Risk management plan (RMP)**

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

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Evrenzo 20 mg film-coated tablets
roxadustat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 20 mg roxadustat.

3. LIST OF EXCIPIENTS

Contains lactose, traces of soya lecithin and Allura Red AC aluminium lake (E129).

4. PHARMACEUTICAL FORM AND CONTENTS

12x1 film-coated tablets
36x1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not chew, break or crush the tablets.
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

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

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1574/001 12 film-coated tablets
EU/1/21/1574/006 36 film-coated tablets

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

evrenzo 20 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Evrenzo 20 mg tablets
roxadustat

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Astellas

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Evrenzo 50 mg film-coated tablets
roxadustat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50 mg roxadustat.

3. LIST OF EXCIPIENTS

Contains lactose, traces of soya lecithin and Allura Red AC aluminium lake (E129).

4. PHARMACEUTICAL FORM AND CONTENTS

12x1 film-coated tablets
36x1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not chew, break or crush the tablets.
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

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

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1574/002 12 film-coated tablets
EU/1/21/1574/007 36 film-coated tablets

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

evrenzo 50 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Evrenzo 50 mg tablets
roxadustat

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Astellas

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Evrenzo 70 mg film-coated tablets
roxadustat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 70 mg roxadustat.

3. LIST OF EXCIPIENTS

Contains lactose, traces of soya lecithin and Allura Red AC aluminium lake (E129).

4. PHARMACEUTICAL FORM AND CONTENTS

12x1 film-coated tablets
36x1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not chew, break or crush the tablets.
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

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

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1574/003 12 film-coated tablets
EU/1/21/1574/008 36 film-coated tablets

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

evrenzo 70 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Evrenzo 70 mg tablets
roxadustat

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Astellas

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Evrenzo 100 mg film-coated tablets
roxadustat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg roxadustat.

3. LIST OF EXCIPIENTS

Contains lactose, traces of soya lecithin and Allura Red AC Aluminium Lake (E129).

4. PHARMACEUTICAL FORM AND CONTENTS

12x1 film-coated tablets
36x1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not chew, break or crush the tablets.
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

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

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1574/004 12 film-coated tablets
EU/1/21/1574/009 36 film-coated tablets

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

evrenzo 100 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Evrenzo 100 mg tablets
roxadustat

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Astellas

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Evrenzo 150 mg film-coated tablets
roxadustat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 150 mg roxadustat.

3. LIST OF EXCIPIENTS

Contains lactose, traces of soya lecithin and Allura Red AC Aluminium Lake (E129).

4. PHARMACEUTICAL FORM AND CONTENTS

12x1 film-coated tablets
36x1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not chew, break or crush the tablets.
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

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

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1574/005 12 film-coated tablets
EU/1/21/1574/010 36 film-coated tablets

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

evrenzo 150 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Evrenzo 150 mg tablets
roxadustat

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Astellas

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Evrenzo 20 mg film-coated tablets
Evrenzo 50 mg film-coated tablets
Evrenzo 70 mg film-coated tablets
Evrenzo 100 mg film-coated tablets
Evrenzo 150 mg film-coated tablets
roxadustat

▼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, or pharmacist.
- 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, or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Evrenzo is and what it is used for

What Evrenzo is
Evrenzo is a medicine that increases the number of red blood cells and haemoglobin level in your blood. It contains the active substance roxadustat.

What Evrenzo is used for
Evrenzo is used to treat adults with symptomatic anaemia that occurs in patients with chronic kidney disease. Anaemia is when you have too few red blood cells and your haemoglobin level is too low. As a result, your body might not receive enough oxygen. Anaemia can cause symptoms such as tiredness, weakness, or shortness of breath.

How Evrenzo works
Roxadustat, the active substance in Evrenzo, works by increasing the level of HIF, a substance in the body which increases the production of red blood cells when oxygen levels are low. By raising HIF levels, the medicine increases the production of red blood cells and raises the levels of haemoglobin (the oxygen-carrying protein in red blood cells). This improves the oxygen supply to your body and may reduce your symptoms of anaemia.

2. What you need to know before you take Evrenzo

Do not take Evrenzo
- if you are allergic to peanut or soya, do not use this medicine. Evrenzo contains soya lecithin.
- if you are allergic to roxadustat or any of the other ingredients of this medicine (listed in section 6).
- if you are more than 6 months pregnant (it is also better to avoid this medicine in early pregnancy - see Pregnancy section).
- if you are breast-feeding.

Warnings and precautions
Talk to your doctor, or pharmacist before taking Evrenzo:

- if you have epilepsy or have ever had convulsions or fits.
- if you have signs and symptoms of an infection, which may include fever, sweating or chills, sore throat, runny nose, shortness of breath, feeling weak, confusion, cough, vomiting, diarrhoea or stomach pain, feeling of burning when you pass urine, red or painful skin or sores on your body.
- if you have a liver disorder.

Chronic kidney disease and anaemia may increase the risk of cardiovascular events and death. Managing your anaemia is important. Your doctor will monitor your haemoglobin and also consider your treatment regimen as anaemia treatment and switching between anaemia treatments may also have a negative impact on your cardiovascular health.

Talk to your doctor, or pharmacist straight away:
- if you get blood clots:
    1. in the veins of your legs (deep vein thrombosis or DVT), signs of which can include pain and/or swelling in the legs, cramping or a feeling of warmth in the affected leg;
    2. in the lungs (pulmonary embolism or PE), signs of which can include sudden shortness of breath, chest pain (usually worse with breathing), feeling of anxiety, dizziness, light-headedness, or fainting; heart racing, coughing (sometimes with blood);
    3. in your haemodialysis access (vascular access thrombosis or VAT) that stop the vascular access from working; signs of this can include swelling, redness, hardening or thickening of the skin around your access, oozing at the access site, not feeling a vibration (“thrill”) over the access area;
- if you have a seizure (convulsion or fit) or possible warning signs that a seizure may occur, such as headache, irritability, fear, confusion or unusual feelings;
- if you have signs and symptoms of an infection, which include fever, sweating or chills, sore throat, runny nose, shortness of breath, feeling weak or faint, confusion, cough, vomiting, diarrhoea, or stomach pain, burning when you pass urine, red or painful skin or sores on your body;
- if you have signs and symptoms of a stroke (cerebrovascular accident), which include sudden weakness or numbness of the face, arm or leg, especially on one side of the body, sudden confusion, trouble speaking or understanding, sudden trouble seeing in one or both eyes, severe headache, loss of consciousness or fainting, seizures (fits), loss of coordination, loss of balance.

Misuse can lead to an increase in blood cells and consequently thicken the blood. This can cause life-threatening problems with the heart or blood vessels.

Children and adolescents
Do not give Evrenzo to children and adolescents aged under 18 years because there is not enough information about its use in this age group.

Other medicines and Evrenzo
Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines. Evrenzo may affect the way these medicines work, or these medicines may affect how Evrenzo works.

In particular, tell your doctor or pharmacist if you have, or are taking any of the following medicines:
- medicines to reduce phosphate levels in your blood (called phosphate binders) or other medicines or supplements that contain calcium, iron, magnesium or aluminium (called multivalent cations), such as sevelamer carbonate or calcium acetate. You must take Evrenzo at least 1 hour after these medicines or supplements. Otherwise roxadustat will not be properly absorbed by your body.
- a medicine to treat gout called probenecid.
- medicines used to lower cholesterol, such as simvastatin, atorvastatin, or rosuvastatin (also called "statins"), or gemfibrozil.
- other medicines used to treat anaemia such as erythropoiesis-stimulating agents (ESAs).

If you normally take any of these medicines, your doctor might change it and prescribe a different medicine for you during your treatment with Evrenzo.

Pregnancy, breast-feeding and fertility
If you are pregnant, think you may be pregnant or are planning to have a baby, contact your doctor. Evrenzo may harm your unborn baby. Evrenzo is not recommended in the first 6 months of pregnancy and must not be taken in the last 3 months of pregnancy. Women taking Evrenzo who are able to become pregnant should use an effective method of contraception during treatment with Evrenzo and for at least one week after the last dose of Evrenzo. If you use a hormonal contraceptive, you must also use a barrier method, such as a condom, or a diaphragm.

Do not breastfeed if you are on treatment with Evrenzo. It is not known if Evrenzo passes into your breast milk and could harm your baby.

Driving and using machines
This medicine may affect your ability to drive or use machines. Seizures can occur as a side effect (see section 4).

Evrenzo contains lactose, soya lecithin and Allura Red AC aluminium lake
Evrenzo contains sugar (lactose), traces of peanut and soya (soya lecithin), and an azo colouring agent (Allura Red AC aluminium lake). If you have been told by your doctor that you have an intolerance to some sugars or are allergic to peanut, soya or azo colouring agents, contact your doctor before taking this medicine.

3. How to take Evrenzo

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

Your doctor will tell you what dose of Evrenzo to take.

Your doctor will check your haemoglobin levels regularly and increase or lower your dose based on your haemoglobin levels.

Evrenzo is taken by mouth as tablets.

Taking Evrenzo
- Take your Evrenzo dose three times per week unless your doctor told you otherwise.
- Never take Evrenzo on consecutive days.
- Take Evrenzo on the same three days every week.

- Evrenzo can be taken with food or between meals.
- Swallow the tablets whole.
- Do not chew, break or crush the tablets.

Take Evrenzo at least 1 hour after you have taken medicines that reduce phosphate levels in your blood (called phosphate binders) or other medicines or supplements that contain calcium, iron, magnesium or aluminium (called multivalent cations).

Dosing Schedule
3 times a week dosing schedule
Evrenzo comes in a blister pack containing medicine for 4 weeks (12 tablets), divided into 4 rows. Each row contains 1 week of medicine (3 tablets). Make sure you take tablets from the same row for each week.

Your dose ranges from 20 mg three times per week up to a maximum 400 mg three times per week.

Different dosing frequencies
In exceptional cases (based upon your haemoglobin levels), your doctor may decide to lower your Evrenzo dose to 20 mg two times or one time per week. In this case your doctor will explain which days week you need to take your dose.

More than 1 tablet needed to make up a dose
In most cases you will have 1 blister package per month. If your dose requires more than 1 blister package, you will need to take a tablet from each blister per dosing day. Your doctor will explain when and how many tablets to take.

Your doctor will monitor your haemoglobin level and may temporarily stop your treatment if your haemoglobin level becomes too high. Do not restart your treatment until your doctor tells you to. Your doctor will tell you what dose of Evrenzo to take and when to start taking it again.

If you take more Evrenzo than you should
If you take more tablets or a higher dose than you should, contact your doctor straight away.

If you forget to take Evrenzo
- Never take a double dose to make up for a forgotten dose.
- If more than 24 hours (1 day) remains before your next scheduled dose, take the missed dose as soon as possible and take the next dose on the next scheduled day.
- If less than 24 hours (1 day) remains before your next scheduled dose: skip the missed dose and take the next dose on the next scheduled day.

If you stop taking Evrenzo
Do not stop taking this medicine unless your doctor tells you to do so.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
Some possible side effects may be serious. Contact your doctor straight away if you get any of the following:
- blood clot in the veins of your legs (deep vein thrombosis or DVT) (may affect up to 1 in 10 people).
- blood clot in the lungs (pulmonary embolism) (may affect up to 1 in 100 people).

- blood clot in your haemodialysis access (vascular access thrombosis or VAT) that causes the vascular access to close up or stop working if you are using a fistula or graft for dialysis access (may affect more than 1 in 10 people).
- stroke (cerebrovascular accident) (may affect up to 1 in 100 people).
- low levels of blood platelets (thrombocytopenia) (may affect up to 1 in 10 people) which may present as unexplained bruising or a rash of small patches of red appearing on the skin (called petechiae), prolonged bleeding from skin cuts, bleeding from the gums or nose, blood in urine or stools, bleeding in the whites of your eyes.
- seizures and warning signs of seizures (convulsions or fits) (may affect up to 1 in 10 people).
- sepsis, a serious or in rare cases, life-threatening infection (may affect up to 1 in 10 people).
- redness and shedding of skin over a larger area of the body, which may be itchy or painful (exfoliative dermatitis) (frequency cannot be estimated from the available data).

Other possible side effects

Very common (may affect more than 1 in 10 people):
- increased amount of potassium
- high blood pressure (hypertension)
- feeling sick (nausea)
- diarrhoea
- swelling due to fluid retention in the extremities (peripheral oedema)

Common (may affect up to 1 in 10 people):
- difficulty in sleeping (insomnia)
- headache
- vomiting
- constipation
- low levels of blood platelets (thrombocytopenia)

Uncommon (may affect up to 1 in 100 people):
- increased amount of bilirubin in your blood

Not known (frequency cannot be estimated from the available data):
- thyroid function decreased
- blood copper increased

Reporting of side effects
If you get any side effects, talk to your doctor, or pharmacist. 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 Evrenzo

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 carton and blister after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

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 Evrenzo contains
Evrenzo 20 mg:
- The active substance is roxadustat. Each tablet contains 20 mg roxadustat.

Evrenzo 50 mg:
- The active substance is roxadustat. Each tablet contains 50 mg roxadustat.

Evrenzo 70 mg:
- The active substance is roxadustat. Each tablet contains 70 mg roxadustat.

Evrenzo 100 mg:
- The active substance is roxadustat. Each tablet contains 100 mg roxadustat.

Evrenzo 150 mg:
- The active substance is roxadustat. Each tablet contains 150 mg roxadustat.

The other ingredients are:
- tablet core: lactose monohydrate, microcrystalline cellulose (E460), croscarmellose sodium (E468), povidone (E1201), magnesium stearate (E470b).

- film-coating: polyvinyl alcohol (E1203), talc (E553b), macrogol (E1521), Allura Red Aluminium Lake AC (E129), titanium dioxide (E171), lecithin (soya) (E322).

What Evrenzo looks like and contents of the pack
Evrenzo 20 mg are red, oval, film-coated tablets, debossed with “20” on one side.
Evrenzo 50 mg are red, oval, film-coated tablets, debossed with “50” on one side.
Evrenzo 70 mg are red, round, film-coated tablets, debossed with “70” on one side.
Evrenzo 100 mg are red, oval, film-coated tablets, debossed with “100” on one side.
Evrenzo 150 mg are red, almond-shaped, film-coated tablets, debossed with “150” on one side.

Evrenzo is available in PVC/aluminium perforated unit dose blisters in packs containing 12 x 1 film-coated tablets and 36 x 1 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

Manufacturer
Delpharm Meppel B.V.
Hogemaat 2
7942 JG Meppel
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Astellas Pharma B.V. Branch
Tél/Tel: +32 (0)2 5580710

Lietuva
Astellas Pharma d.o.o.
Tel.: +370 37 408 681

България
Астелас Фарма ЕООД
Тел.: +359 2 862 53 72

Česká republika
Astellas Pharma s.r.o.
Tel: +420 221 401 500

Danmark
Astellas Pharma a/s
Tlf: +45 43 430355

Deutschland
Astellas Pharma GmbH
Tel.: +49 (0)89 454401

Eesti
Astellas Pharma d.o.o.
Tel: +372 6 056 014

Ελλάδα
Astellas Pharmaceuticals AEBE
Τηλ: +30 210 8189900

España
Astellas Pharma S.A.
Tel: +34 91 4952700

France
Astellas Pharma S.A.S.
Tél: +33 (0)1 55917500

Hrvatska
Astellas d.o.o.
Tel: +385 1670 0102

Ireland
Astellas Pharma Co. Ltd.
Tel: +353 (0)1 4671555

Ísland
Vistor hf
Sími: +354 535 7000

Italia
Astellas Pharma S.p.A.
Tel: +39 (0)2 921381

Κύπρος
Ελλάδα
Astellas Pharmaceuticals AEBE
Τηλ: +30 210 8189900

Luxembourg/Luxemburg
Astellas Pharma B.V. Branch
Belgique/Belgien
Tél/Tel: +32 (0)2 5580710

Magyarország
Astellas Pharma Kft.
Tel.: +36 1 577 8200

Malta
Astellas Pharmaceuticals AEBE
Tel: +30 210 8189900

Nederland
Astellas Pharma B.V.
Tel: +31 (0)71 5455745

Norge
Astellas Pharma
Tlf: +47 66 76 46 00

Österreich
Astellas Pharma Ges.m.b.H.
Tel.: +43 (0)1 8772668

Polska
Astellas Pharma Sp.z.o.o.
Tel.: +48 225451 111

Portugal
Astellas Farma, Lda.
Tel: +351 21 4401300

România
S.C. Astellas Pharma SRL
Tel: +40 (0)21 361 04 95

Slovenija
Astellas Pharma d.o.o.
Tel: +386 14011400

Slovenská republika
Astellas Pharma s.r.o.
Tel: +421 2 4444 2157

Suomi/Finland
Astellas Pharma
Puh/Tel: +358 (0)9 85606000

Sverige
Astellas Pharma AB
Tel: +46 (0)40-650 15 00

Latvija
Astellas Pharma d.o.o.
Tel: +371 67 619365

United Kingdom (Northern Ireland)
Astellas Pharma Co., Limited
Tel: +353 (0)1 4671555
Free call from Northern Ireland: 0800 783 5018

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

Annex IV

Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for roxadustat, the scientific conclusions of PRAC are as follows:

In view of available data on Ischemic central nervous system vascular conditions from clinical trial(s), the literature, spontaneous reports including in some cases a close temporal relationship, a positive dechallenge and rechallenge and in view of a plausible mechanism of action, the PRAC Rapporteur considers a causal relationship between roxadustat and Cerebral infarction is at least a reasonable possibility. The PRAC Rapporteur concluded that the product information of products containing roxadustat should be amended accordingly. Furthermore, based on the expressed concerns of the MAH that current information presented in the PIL on Thrombocytopenia may suggest that the symptoms listed in the section 4 may affect up to 1 in 10 people, the PRAC Rapporteur concluded that the product information of products containing roxadustat should be amended to avoid this misinterpretation.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for roxadustat the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing roxadustat is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.