SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

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

Contains lactose monohydrate (sugar).

Evrenzo 20 mg film-coated tablets

Each tablet contains 20 mg of roxadustat.

Excipient with known effect: 42,6 mg of lactose monohydrate per tablet.

The film coating contains 0,9 mg of Allura Red AC aluminum lake.

Evrenzo 50 mg film-coated tablets

Each tablet contains 50 mg of roxadustat.

Excipient with known effect: 106,5 mg of lactose monohydrate per tablet.

The film coating contains 1,7 mg of Allura Red AC aluminum lake.

Evrenzo 70 mg film-coated tablets

Each tablet contains 70 mg of roxadustat.

Excipient with known effect: 149,1 mg of lactose monohydrate per tablet.

The film coating contains 2,1 mg of Allura Red AC aluminum lake.

Evrenzo 100 mg film-coated tablets

Each tablet contains 100 mg of roxadustat.

Excipient with known effect: 213,0 mg of lactose monohydrate per tablet.

The film coating contains 2,8 mg of Allura Red AC aluminum lake.

Evrenzo 150 mg film-coated tablets

Each tablet contains 150 mg of roxadustat.

Excipient with known effect: 319,5 mg of lactose monohydrate per tablet.

The film coating contains 3,7 mg of Allura Red AC aluminum lake.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Evrenzo 20 mg tablets

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

Evrenzo 50 mg tablets

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

Evrenzo 70 mg tablets

Red, round tablets (9 mm) with ‘70’ debossed on one side.

Evrenzo 100 mg tablets

Red, oval tablets (14 mm × 7 mm) with ‘100’ debossed on one side.

Evrenzo 150 mg tablets

Red, almond-shaped tablets (14 mm × 9 mm) with ‘150’ debossed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Leave the blisters in the carton until required for use.

Treatment with Evrenzo should be initiated by a medical practitioner experienced in the management of anaemia.

Posology

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

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

Starting dose at treatment initiation

Adequate iron stores should be ensured prior to initiating treatment with Evrenzo.

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 Evrenzo 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 Erythropoiesis Stimulating Agent (ESA)

For patients converting anaemia therapy from ESA to roxadustat, the recommended starting dose of Evrenzo 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 Evrenzo 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	> 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

Dose adjustment and haemoglobin monitoring

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

The dose of Evrenzo can be adjusted stepwise up or down from the starting dose 4 weeks after treatment start, and every 4 weeks thereafter. When adjusting the dose of Evrenzo, consider the current haemoglobin level and the recent rate of change in haemoglobin 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 patients on dialysis).

Table 2: Dose adjustment rules

Change in Hb over the previous 4 weeks*	**Current haemoglobin (Hb) level (g/dL):** **Lower than 10,5**	**10,5 to 11,9**	**12,0 to 12,9**	**13,0 or higher**
Change is 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 is value between -1,0 and +1,0 g/dL	Increase dose by one step	No change	Reduce dose by one step	

Change is value of less than -1,0 g/dL	Increase dose by one step	Increase dose by one step	No change

The dose of Evrenzo should not be adjusted more frequently than once every 4 weeks, except if haemoglobin (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.

*Change in 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 haemoglobin levels between 10 to 12 g/dL, the haemoglobin levels should continue to be monitored regularly and the dose adjustment rules must be 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

haemoglobin levels should be monitored and the dose adjustment rules must be followed (see Table 2; see also section 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 an Evrenzo 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 Evrenzo dose, the missed dose must be skipped and the next Evrenzo dose must be taken on the next scheduled day. In each case, the regular dosing schedule should be resumed thereafter.

Special populations

Paediatric population

Safety and efficacy of roxadustat in paediatric patients under 18 years of age have not been established. Evrenzo should therefore not be used in children (see section 4.3).

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 section 4.4 and 5.2).

The safety and efficacy of roxadustat have not been studied in CKD patients with concurrent moderate or severe hepatic impairment (Child-Pugh class B and C). Caution is recommended when prescribing roxadustat to CKD patients with concurrent moderate or severe hepatic impairment. Consider using a lower starting dose in these patients (see sections 4.4 and 5.2).

Method of administration

Evrenzo tablets are taken orally with or without food. The tablets must be swallowed whole and not chewed, broken or crushed.

The tablets should be taken at least 1 hour before or 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).

The tablets can be taken before or after dialysis (see section 5.2).

4.3 Contraindications

Evrenzo is contraindicated in the following conditions:

- Hypersensitivity to roxadustat or to any of the excipients (see section 6.1).
- Breastfeeding (see sections 4.6 and 5.3).
- Pregnancy (see sections 4.6 and 5.3).
- Children under 18 years (see section 4.2).

4.4 Special warnings and precautions for use

Vascular Access Thrombosis (VAT)

Vascular access thrombosis was reported as very common amongst the patients on dialysis in clinical trials (see section 4.8).

In patients on dialysis rates of VAT in Evrenzo-treated patients were highest in the first 12 weeks following initiation of Evrenzo, at haemoglobin values more than 12 g/dL and in the setting of haemoglobin rise of more than 2 g/dL over 4 weeks.

Closely monitor haemoglobin levels and adjust the dose of Evrenzo using the dose adjustment rules (see Table 2) to avoid haemoglobin levels of more than 12 g/dL and haemoglobin rise of more than 2 g/dL over 4 weeks.
Patients with VAT should be evaluated and treated according to standard of care. The effect of interrupting or discontinuing roxadustat in this setting is unknown.

Seizures

Seizures were reported as common amongst the patients in clinical trials receiving Evrenzo (see section 4.8).

Evrenzo 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 CNS infections. The effect of interrupting or discontinuing roxadustat in this setting is unknown.

Serious infections

Patients with signs and symptoms of an infection should be promptly evaluated and treated according to standard of care.

In patients not on dialysis serious infections occurred in 18,9 % (12,4 patients with events per 100 patient years of exposure) in the Evrenzo group and 12,9 % (10,6 patients with events per 100 patient years of exposure) in the placebo group. Fatal infections occurred in 3,0 % (1,8 patients with events per 100 patient years of exposure) in the Evrenzo group vs 1,0 % (0,7 patients with events per 100 patient years of exposure) in the placebo group.

The most commonly reported serious infections were pneumonia, sepsis and urinary tract infections.

In patients on dialysis the numerical imbalance of serious and fatal infections was not observed between patients treated with Evrenzo and patients treated with ESAs.

A causal relationship between Evrenzo and serious infections has not been established.

Deep Vein Thrombosis (DVT)

Deep vein thrombosis was reported as common amongst the patients in clinical trials (see section 4.8).

The majority of DVT events were serious.

Patients with signs and symptoms of DVT should be promptly evaluated and treated according to standard of care. The effect of interrupting or discontinuing Evrenzo in this setting is unknown.

Hepatic impairment

The safety and efficacy of Evrenzo have not been confirmed in patients with CKD and moderate or severe hepatic impairment (Child-Pugh class B and C) (see section 4.2).

Excipients

Evrenzo contains lactose monohydrate (sugar). Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Evrenzo contains Allura Red AC aluminium lake (see section 6.1) which may cause allergic reactions.

4.5 Interaction with other medicines and other forms of interaction

Effect of other medicines on Evrenzo

Phosphate binders and other products containing multivalent cations

Co-administration of Evrenzo with sevelamer carbonate or calcium acetate decreased the plasma exposure of Evrenzo (see section 5.2). Evrenzo should be taken at least 1 hour before or after administration of phosphate binders or other medicines or supplements containing multivalent cations such as calcium, iron, magnesium or aluminium (see section 4.2). This restriction does not apply to lanthanum carbonate, as the co-administration of Evrenzo with

lanthanum carbonate did not result in a clinically meaningful change in the plasma exposure of roxadustat.

Modifiers of CYP2C8 activity

Co-administration of Evrenzo with gemfibrozil, an inhibitor of CYP2C8 and OATP1B1, increased the plasma exposure of roxadustat (see section 5.2). Monitor haemoglobin levels when initiating or discontinuing concomitant treatment with gemfibrozil or other strong inhibitors or inducers of CYP2C8. Adjust the dose of Evrenzo following dose adjustment rules (see Table 2) based on haemoglobin monitoring.

Modifiers of UGT1A9 activity

Roxadustat is a substrate of UGT1A9. Co-administration of Evrenzo with probenecid, an inhibitor of UGT and OAT1/OAT3, increased the plasma exposure of roxadustat (see section 5.2). Monitor haemoglobin levels when initiating or discontinuing concomitant treatment with probenecid or other inhibitors of UGT1A9. Adjust the dose of Evrenzo following dose adjustment rules (see Table 2) based on haemoglobin monitoring.

<u>Effects of Evrenzo on other medicines</u>

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 Evrenzo with simvastatin, rosuvastatin or atorvastatin increased the plasma exposure of each of the statins by 2- to 3-fold (see section 5.2). Interactions are also expected with other statins. When co-administered with Evrenzo, 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.

Evrenzo may increase the plasma exposure of other medicines that are substrates of BCRP or OATP1B1. Monitor for possible adverse reactions of co-administered medicines and adjust dose accordingly.

Evrenzo and ESAs

Evrenzo has not been studied in combination with ESAs.

4.6 Fertility, pregnancy and lactation

Pregnancy, women of childbearing potential and contraception

Evrenzo is contraindicated for use in pregnant women and females of reproductive potential not using effective contraception because of the potential for foetal harm based on animal data (see section 4.3 and section 5.3). There are currently no human data to establish the presence or absence of drug-associated risk with the use of Evrenzo during pregnancy.

Breastfeeding

Women must not breastfeed during treatment with Evrenzo (see section 5.3), because of the potential for adverse reactions from Evrenzo in a breastfed infant.

Fertility

Women of reproductive potential should use effective contraception for at least one week prior to start with Evrenzo and until after the last dose of Evrenzo is taken. At a maternally toxic dose, increased embryonic loss was observed (see section 5.3).

4.7 Effects on ability to drive and use machines

Evrenzo has negligible influence on the ability to drive and use machines. However, it can cause seizures and dizziness. Therefore, patients should not drive or operate machinery when using Evrenzo (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The total safety database from clinical trials comprised 13 063 subjects (CKD patients and healthy volunteers), including 7 821 subjects treated with Evrenzo, 3 129 with ESAs and 2 113 with placebo. In the non-dialysis controlled Phase 3 studies 3 154 CKD patients were treated with Evrenzo (4 641 PEY) versus 1 935 with placebo and 423 with ESAs. In dialysis phase 3 studies 3 004 CKD patients were treated with Evrenzo (4 341 PEY) versus 2 612 with ESAs.

Identified adverse reactions associated with Evrenzo are vascular access thrombosis (VAT), seizures, deep vein thrombosis (DVT) and nausea.

Tabulated list of adverse drug reactions

Adverse drug reactions in Table 3 are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: 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).

Table 3: Adverse drug reactions following treatment with Evrenzo

System Organ Class (MedDRA)	**Frequency category**	**Adverse drug reaction**
Nervous System Disorders	Common	Seizures
Gastrointestinal Disorders	Common	Nausea
Vascular Disorders	Very Common Common	Vascular Access Thrombosis (VAT) Deep Vein Thrombosis (DVT)

Description of selected adverse reactions

Vascular Access Thrombosis (VAT)

Vascular access thrombosis was reported as very common amongst the patients on dialysis in clinical trials. Haemoglobin levels must be monitored closely (see section 4.4).

In patients on dialysis, vascular access thrombosis was observed in 12,8 % (7,6 patients with events per 100 patient years of exposure) in the Evrenzo group, compared to 10,2 % (5,4 patients with events per 100 patient years of exposure) in the ESA group.

Seizures

Seizures were reported as common amongst the patients in clinical trials receiving Evrenzo (see section 4.4).

In patients not on dialysis, seizures occurred in 1,1 % (0,6 patients with events per 100 patient years of exposure) in the Evrenzo group, and 0,2 % (0,2 patients with events per 100 patient years of exposure) in the placebo group.

In patients on dialysis, seizures occurred in 2,0 % (1,2 patients with events per 100 patient years of exposure) in the Evrenzo group, and 1,6 % (0,8 patients with events per 100 patient years of exposure) in the ESA group.

Deep vein thrombosis (DVT)

Deep vein thrombosis was reported as common amongst the patients in clinical trials. The majority of DVT events were serious.

In 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 Evrenzo group, and 0,2 % (0,2 patients with events per 100 patient years of exposure) in the placebo group.

In patients on dialysis, DVT events occurred in 1,3 % (0,8 patients with events per 100 patient years of exposure) in the Evrenzo group and 0,3 % (0,1 patients with events per 100 patient years of exposure) in the ESA group.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are

asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online on SAHPRA's website:

https://primaryreporting.who-umc.org/Reporting/Reporter?OrganizationID=ZA

or

Astellas Pharma (Pty) Ltd., 7 Mirage Road, Bedfordview, 2007, South Africa

Tel: +27 11 615 9433

Mobile: +27 82 410 8864

Email-: drugsafety.za@astellas.com

4.9 Overdose

Single supratherapeutic doses of Evrenzo 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. Evrenzo overdose can elevate haemoglobin levels above the desired level (10-12 g/dL), which should be managed with discontinuation or reduction of Evrenzo dosage (see section 4.2) and careful monitoring and treatment as clinically indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other anti-anaemic preparations

ATC code: B03XA05.

Mechanism of action

Hypoxia inducible factor (HIF) is 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. Roxadustat mimics the body's natural response to hypoxia by reversibly inhibiting HIF-prolyl hydroxylases (PH) enzymes that target HIFs for degradation under normal oxygen conditions.

Through the 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. This results in improved iron bioavailability, increased haemoglobin production and increased red cell mass.

Pharmacodynamic effects

Haemoglobin

Roxadustat is effective in increasing and maintaining haemoglobin concentrations in patients with CKD anaemia. Roxadustat corrects and maintains haemoglobin levels in patients who have not been previously treated with ESA and maintains haemoglobin levels in patients converting from existing ESA therapy.

Erythropoietin

Roxadustat produces a dose-dependent increase in endogenous plasma erythropoietin levels, with peak levels reached at 8 to 12 hours post-dose.

Hepcidin

Hepcidin, an iron metabolism regulating protein, is increased during inflammation and contributes to a reduced iron availability and therefore inadequate erythropoiesis. Clinical data consistently demonstrated that roxadustat lowers hepcidin, improves iron utilisation, absorption and bioavailability, and is effective without requirement for routine use of intravenous (IV) iron.

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 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.

Effects on blood pressure

There is no clinically meaningful effect of roxadustat on blood pressure and roxadustat does not exacerbate existing hypertension or increase episodes of hypertensive emergency.

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 multicenter and randomised studies in non-dialysis dependent (NDD; against placebo and darbepoetin alfa) and dialysis-dependent (DD; against ESA) CKD patients with anaemia.

Efficacy results

Course of haemoglobin during treatment

In clinical studies, roxadustat was effective in achieving and maintaining target haemoglobin levels (10-12 g/dL) in patients with CKD anaemia not on dialysis, as well as CKD patients on dialysis, irrespective of prior ESA treatment.

In NDD patients in need of anaemia treatment for haemoglobin correction, the proportion of patients who achieved haemoglobin 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 haemoglobin from baseline to weeks 28 to 36 in the roxadustat group (1,91 g/dL) compared with placebo (0,14 g/dL). These results show superiority of roxadustat over placebo. In the NDD studies, an increase in haemoglobin of at least 1 g/dL was achieved with a median time of 4,1 weeks.

The results of the key efficacy endpoints in the roxadustat groups in ESA-controlled NDD Study, which evaluated patients in need of anaemia treatment for haemoglobin correction, were comparable with those observed in the roxadustat group of the NDD pool, also confirming the effect of roxadustat.

In DD patients in need of anaemia treatment for haemoglobin correction and those converted from ESA treatment, there was an increase in haemoglobin from baseline to weeks 28 to 36 in the roxadustat group; this increase was comparable to that observed in the ESA group. These

results show noninferiority of roxadustat to ESA. The proportion of patients who achieved haemoglobin response during the first 24 weeks was similar in the roxadustat and ESA groups.

Rescue therapy, RBC transfusion, intravenous iron and LDL cholesterol

Treatment with roxadustat resulted in a reduced use of RBC transfusions and IV iron supplementation compared with ESA.

Roxadustat was effective without requirement for routine use of intravenous iron

Roxadustat reduced hepcidin leading to an increased iron mobilization, as demonstrated by reduced ferritin, increased serum iron and stable transferrin saturation values, which were assessed over time as indicators of iron status.

There was a reduction in mean low density lipoprotein (LDL) cholesterol in roxadustat-treated patients compared with placebo or ESA-treated patients. This change was observed regardless of the use of statins.

Inflammation

Roxadustat was effective in increasing and/or maintaining haemoglobin levels regardless of inflammation status as measured by hs-CRP levels. The dose requirement of roxadustat was not impacted by inflammation and the effect of roxadustat was maintained over time as mean haemoglobin levels are maintained.

Iron repletion status

Roxadustat increased and/or maintained haemoglobin levels regardless of baseline iron-repletion status.

Patient reported outcomes not on dialysis

Pooled analyses of non-dialysis roxadustat versus placebo patients showed statistically significantly higher improvement from baseline to week 12 in roxadustat compared to placebo in health-related quality-of-life domains relevant to CKD anaemia that capture symptoms of fatigue, low energy and weakness, the severities of which vary with the degree of anaemia. Improvements were seen in SF-36 physical functioning subscore (p=0,031), SF-36 Vitality subscore (p<0,001), FACT-An total score (p=0,005), and FACT-An anaemia subscale score (nominal p<0,001). Also for EQ-5D-5L VAS score a statistically significant improvement was observed compared to placebo.

For the ESA-controlled NDD study noninferiority of roxadustat to darbepoetin was established with regards to SF-36 PF and SF-36 VT. In both treatment groups there was a numerical improvement from baseline for the two SF-36 domains in weeks 12-28.

Patient reported outcomes on dialysis

In the DD studies, the observed QoL changes from baseline within each treatment group were numerically comparable between the roxadustat and ESA groups.

Clinical safety

Safety of roxadustat was primarily assessed using pooled phase 3 data analyses as described above. The safety profile observed in the roxadustat development program is reflective of the CKD populations. The general safety of roxadustat was overall comparable to placebo and ESA for the majority of the safety variables evaluated and generally similar across subgroups (see section 4.8).

Cardiovascular safety

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 hospitalization for either unstable angina or congestive heart failure), from the phase 3 study program was conducted in 8984 patients.

In the NDD pool 4 270 patients (2 386 on roxadustat and 1 884 on placebo) were analysed separately from 4 714 patients in the DD pool (2 354 on roxadustat and 2 360 on ESA). In both pools, the cardiovascular risk of roxadustat was compared versus placebo (NDD) or ESA (DD) using the pooled hazard ratio (HR) and its 95 % confidence interval (CI) and noninferiority of roxadustat versus comparator was tested using noninferiority margins of 1,8 and 1,3.
In addition, HRs and CIs were calculated for MACE and MACE+ data in the ESA-controlled NDD study.

MACE and MACE+ in non-dialysis-dependent patients

In NDD patients the analysis for MACE and MACE+ which included all data from the start of study treatment until the end of posttreatment safety follow-up (ITT), showed HRs of 1,08 and 1,04, with upper limits of the 95 % CIs of 1,24 and 1,18, below both the 1,8 and 1,3 noninferiority margins. The outcomes support noninferiority of the cardiovascular safety of a treatment strategy starting with roxadustat compared with a treatment strategy starting with placebo.
In a darbepoetin alfa controlled study results of on-treatment and ITT analyses for MACE and MACE+ showed HR point estimates between 0,81 and 0,93, with upper limits of the 95 % CIs

between 1,25 and 1,33, which do not suggest an increased CV risk of roxadustat versus darbepoetin alfa.

MACE and MACE+ in dialysis-dependent patients

In DD patients analysis results for MACE and MACE+ observed on treatment showed HRs of 1,09 and 0,98, with upper limits of the 95 % CIs for HRs of 1,26 and 1,11 respectively, below both the 1,8 and 1,3 noninferiority margins. Noninferiority regarding cardiovascular safety of roxadustat based on MACE and MACE+ was established in CKD DD patients treated with roxadustat versus those treated with ESA.

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 and protein binding

Roxadustat is highly bound to human plasma proteins (approximately 99 %), predominantly to albumin.

Elimination

The mean effective half-life ($t_{1/2}$) of roxadustat is approximately 15 hours in patients with CKD. The main elimination pathway of roxadustat is metabolism, primarily mediated by CYP2C8 and UGT1A9 (*in vitro* assays). Roxadustat is primarily metabolized 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.

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.

Excretion

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, sex, race, body weight, renal function (eGFR) or dialysis status in patients with anaemia due to CKD.

Haemodialysis

In dialysis-dependent 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 interactions

In Vitro assessment of drug interactions

Roxadustat is a substrate for CYP2C8 and UGT1A9 enzymes, as well as BCRP, OATP1B1, OAT1 and OAT3. Roxadustat is an inhibitor of CYP2C8, BCRP, OATP1B1 and OAT3. Roxadustat showed no inhibition of other CYP metabolizing enzymes or transporters, or induction of CYP enzymes at clinically relevant concentrations.

Effects of other medicines on roxadustat

Co-administration with gemfibrozil (CYP2C8 and OATP1B1 inhibitor) or probenecid (UGT and OAT inhibitor) in healthy subjects increased roxadustat AUC by 2,3-fold and C_{max} by 1.4-fold (see section 4.5).

Co-administration of roxadustat with the 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 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 healthy subjects and based on a population pharmacokinetic analysis in patients with CKD.

Drug interaction studies conducted in healthy subjects indicated no clinically significant effect of lanthanum carbonate, oral adsorptive charcoal or omeprazole on roxadustat pharmacokinetics. Population pharmacokinetic analysis in patients with CKD showed no effect of clopidogrel on roxadustat exposure.

Effects of roxadustat on other medicines

Co-administration 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 roxadustat with rosuvastatin increased the AUC and C_{max} of rosuvastatin 2,9- and 4,5-fold, respectively. Co-administration of roxadustat with atorvastatin increased the AUC and C_{max} of atorvastatin 2,0- and 1,3-fold, respectively.

Roxadustat may also increase the exposure of other statins (see section 4.5).

The pharmacokinetics of bupropion, rosiglitazone and S-warfarin (probe substrates for CYP2B6, CYP2C8 and CYP2C9, respectively) were not affected by co-administration with roxadustat.

5.3 Preclinical safety data

Carcinogenicity and mutagenicity

There was no carcinogenicity or mutagenicity signal in animal studies, suggesting that roxadustat does not represent a genotoxic risk in humans. Roxadustat did not induce tumours in either mice or rats at any of the doses evaluated in 2-year carcinogenicity studies. Oral doses in mice consisted of 15, 30 and 60 mg/kg three times per week, and oral doses in rat were 2.5, ~~5~~ 5 and 10 mg/kg three times per week. The exposure at the highest doses evaluated in mice and rats were approximately two times the human exposure at the Maximum Recommended Human Dose (MRHD).

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 doses up to 500 mg/kg.

Reproductive and developmental toxicity

Roxadustat had no effect on mating or fertility in treated male or female rats at doses up to 30 mg/kg (approximately four times the human exposure at the MRHD). In female rats there

were increases in the number of nonviable 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.

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 a dose of 30 mg/kg (approximately six times the exposure at the MRHD).

Other effects

Exaggerated pharmacology resulting in excessive erythropoiesis has been observed in repeated-dose toxicity studies in healthy animals. In rats, high red blood cell count and haematocrit (>68 %) were associated with tissue congestion and clot formation on the heart valves with consequent thromboembolic events at doses from 15 mg/kg (approximately two times the human exposure at MRHD). Increases in erythropoiesis were also observed in monkeys without toxicity at doses up to 30 mg/kg (approximately equivalent to the human exposure at MRHD). High red blood cell count and/or haematocrit are very unlikely during clinical use in patients, since the posology is based on control and maintenance of haemoglobin levels well below those that occurred in the animals in toxicity studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate

Cellulose, microcrystalline

Croscarmellose sodium

Povidone

Magnesium stearate

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

3 years

6.4 Special precautions for storage

Store below 30°C.

Store in the original package.

KEEP OUT OF REACH OF CHILDREN.

Leave the blisters in the carton until required for use.

6.5 Nature and contents of container

PVC/aluminium blisters in a carton containing 12 tablets.

6.6 Special precautions for disposal

No special requirements for disposal.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Astellas Pharma (Pty) Ltd., 7 Mirage Road, Bedfordview, 2007, South Africa

8. REGISTRATION NUMBER(S)

Evrenzo 20 mg: 55/8.5/0417

Evrenzo 50 mg: 55/8.5/0418

Evrenzo 70 mg: 55/8.5/0419

Evrenzo 100 mg: 55/8.5/0420

Evrenzo 150 mg: 55/8.5/0421

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 July 2022

Date of latest renewal:

10. DATE OF REVISION OF THE TEXT