Roxudo™

(ROXADUSTAT)

Tablet

روکسوڈو

COMPOSITION:
Roxudo Tablet 20 mg:
Each film coated tablet contains:
Roxadustat ..... 20 mg.

Product Specs.: Innovator

Roxudo Tablet 50 mg:
Each film coated tablet contains:
Roxadustat ..... 50 mg.

Product Specs.: Innovator

Roxudo Tablet 70 mg:
Each film coated tablet contains:
Roxadustat ..... 70 mg.

Product Specs.: Innovator

Roxudo Tablet 100 mg:
Each film coated tablet contains:
Roxadustat ..... 100 mg.

Product Specs.: Innovator

Roxudo Tablet 150 mg:
Each film coated tablet contains:
Roxadustat ..... 150 mg.

Product Specs.: Innovator

CLINICAL PHARMACOLOGY: Pharmacotherapeutic group: Anti-anemic preparations, other anti-anemic 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.
Pharmacokinetics:
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.
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.
Elimination: The mean effective half-life (t½) 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 hemodialysis. Specific Populations: 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 anemia due to CKD.
Patients on hemodialysis: 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 hemodialysis. Dialysis is a negligible route of overall clearance of Roxadustat.
Patients with 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.

INDICATIONS AND USAGE:
Roxadustat is indicated for treatment of adult patients with symptomatic anemias associated with chronic kidney disease (CKD).

DOSAGE AND ADMINISTRATION:
The appropriate dose of Roxadustat must be taken orally three times per week and not on consecutive days. The dose should be individualized 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.
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 anemia 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.

DOSE RECOMMENDATIONS:
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 5000	Less than 80	70
25 to Less than 40	5000 up to 8000	80 up to and inlcuding 120	100
40 up to and inlcuding 80	More than 8000 up to and including 16000	More than 120 up to and including 200	150
More than 80	More than 16000	More than 200	200

ESA: Erythropoiesis-stimulating agent
Dose adjustment and Hb monitoring: The individualized 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 stabilized, 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).
Tablet 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 stabilization 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.
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.

METHOD OF ADMINISTRATION:
Roxadustat film-coated tablets are to be taken orally with or without food. Tablets are to be swallowed whole and not chewed, broken or crushed. 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 aluminum.

CONTRAINDICATIONS:
Roxadustat is contraindicated in the following conditions:
- Hypersensitivity to the active substance, peanut, soya or to any of the excipients listed
- Third trimester of pregnancy
- Breast-feeding

WARNINGS AND PRECAUTIONS:
Cardiovascular and mortality risk Overall, the cardiovascular and mortality risk for treatment with Roxadustat has been estimated to be comparable to the cardiovascular and mortality risk for ESA therapy based on data from direct comparison of both therapies.
Thrombotic vascular events: The reported risk of thrombotic vascular events (TVEs) should be carefully weighed against the benefits to be derived from treatment with Roxadustat particularly in patients with pre-existing risk factors for TVE, including obesity and prior history of TVEs (e.g., deep vein thrombosis [DVT] and pulmonary embolism [PE]). Patients with signs and symptoms of TVEs should be promptly evaluated and treated according to standard of care. The decision to interrupt or discontinue treatment should be based on a benefit-risk consideration for the individual patient.
Seizures: 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. 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, hemolysis, severe aluminum toxicity, underlying hematologic 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, Roxadustat should not be continued beyond 24 weeks of therapy.

DRUG INTERACTIONS:
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 8 containing calcium, iron, magnesium or aluminum. Roxadustat should be taken at least 1 hour after administration of phosphate binders or other medicinal products or supplements containing multivalent cations. 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.
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.
Roxadustat and ESAs: It is not recommended to combine administration of Roxadustat and ESAs as the combination has not been studied

USE IN SPECIFIC POPULATIONS:
Pregnancy: Roxadustat should not be initiated in women planning on becoming pregnant, during pregnancy or when anemia associated with CKD is diagnosed during pregnancy. In such cases, alternative therapy should be started, if appropriate. There are no data on the use of Roxadustat in pregnant women. Studies in animals have shown reproductive toxicity. Roxadustat is contraindicated during the third trimester of pregnancy and is not recommended during the first and second trimester of pregnancy.
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 Roxadustat.
Breast-feeding: It is unknown whether Roxadustat/metabolites are excreted in human milk. Available animal data have shown excretion of Roxadustat in milk hence it is contraindicated during breast-feeding.
Pediatric use: Safety and efficacy of Roxadustat in pediatric patients under 18 years of age have not been established. No data are available.
Geriatric use: No adjustment of the starting dose is required in elderly patients.
Patients with hepatic impairment: No adjustment of the starting dose level is required in patients with mild hepatic impairment (Child-Pugh class A). 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). Roxadustat 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.

ADVERSE REACTIONS:
The most frequent (≥10%) adverse reactions associated with Roxadustat are hypertension (13.9%), vascular access thrombosis (12.8%), diarrhea (11.8%), peripheral oedema (11.7%), hyperkalemia (10.9%) and nausea (10.2%). The most frequent (≥1%) serious adverse reactions associated with Roxadustat were sepsis (3.4%), hyperkalemia (2.5%), hypertension (1.4%) and deep vein thrombosis (1.2%).
Other common side effects include Constipation, vomiting, headache, insomnia. Uncommon include: Hyperbilirubinemia, Pulmonary embolism. Not known: Dermatitis Exfoliative Generalized, Secondary hypothyroidism.

OVERDOSAGE:
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 hemodialysis.

INSTRUCTIONS:
- Store below 30ºC.
- Protect from heat, sunlight & moisture.
- Keep out of the reach of children.
- To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:
Roxudo Tablet 20 mg : Pack of 1 x 12 tablets.
Roxudo Tablet 50 mg : Pack of 2 x 6 tablets.
Roxudo Tablet 70 mg : Pack of 2 x 6 tablets.
Roxudo Tablet 100 mg : Pack of 2 x 6 tablets.

ہدایات:
۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

FOR FURTHER INFORMATIONS PLEASE CONTACT:

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