Renvista

Roxadustat INN

Composition:
Renvista 20 Tablet: Each film-coated tablet contains Roxadustat INN 20 mg.
Renvista 50 Tablet: Each film-coated tablet contains Roxadustat INN 50 mg.
Renvista 100 Tablet: Each film-coated tablet contains Roxadustat INN 100 mg.

Pharmacology:
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.

Indication:
Renvista (Roxadustat) is indicated for the treatment of adult patients with symptomatic anaemia associated with chronic kidney disease (CKD).

Dosage & Administration:
The appropriate dose of Roxadustat must be taken orally three times per week and not on consecutive days.
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 adults, the usual starting dose is 50 mg three times weekly. 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:
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.

Starting doses of Roxadustat to be taken three times per week in patients converting from an ESA:

(Table-1)

Darbepoetin alfa intravenous or subcutaneous dose (mcg/week)	Epoetin intravenous or subcutaneous dose (IU/week)	Methoxy polyethylene glycol-epoetin beta intravenous or subcutaneous dose (mcg/monthly)	Roxadustat dose (mg 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 including 120	100
40 up to and including 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 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.
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.

Maitenance 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 in 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.

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.

Contraindications:
Roxadustat is contraindicated in the following conditions like;
- Hypersensitivity to the active ingredient, peanut, soya, or any excipients of the finished product.
- Third trimester of pregnancy
- Breast-feeding

Warnings and Precautions:
Hepatic impairment: Caution is warranted when Roxadustat is administered to patients with moderate hepatic impairment. Roxadustat is not recommended for use in patients with severe hepatic impairment.
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. Women of childbearing potential must use highly effective contraception during treatment and for at least one week after the last dose of Roxadustat.
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.
Seizures: Seizures were reported as common amongst the patients in clinical studies receiving Roxadustat. 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.

Side Effects:
The most common side effects of Roxadustat tablet include: nausea, high blood pressure, diarrhoea, peripheral edema, insomnia, headache, vomiting, constipation. There are also some possible side effects including: blood clots in veins of the legs, blood clots in lungs, seizures etc.

Drug Interaction:
Roxadustat is an inhibitor of CYP2C8, BCRP, OATP1B1 and OAT3. 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. Clopidogrel has no effect on Roxadustat exposure in patients with CKD.

Use in Special Population:
Pregnancy: There are no data on the use of Roxadustat in pregnant women. Studies in animals have shown reproductive toxicity. If pregnancy occurs while Roxadustat is being administered, treatment should be discontinued and switched to alternative treatments, if appropriate.
Breast-feeding: It is unknown whether Roxadustat/metabolites are excreted in human milk. Roxadustat is contraindicated during breast-feeding.
Fertility: In animal studies, there were no effects of Roxadustat on male and female fertility.

Overdosage:
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. 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.

Storage:
- Store below 30^0 C, keep in dry place & protect from light.
- Keep out of the reach of children.

Packing:
Renvista 20 Tablet: Each box contains 3 tablets in Alu-Alu blister pack.
Renvista 50 Tablet: Each box contains 3 tablets in Alu-Alu blister pack.
Renvista 100 Tablet: Each box contains 3 tablets in Alu-Alu blister pack.

Manufactured by:
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