Oroxat™
Roxadustat INN Film Coated Tablet

Description:
Oroxat™ is a first-in-class, orally administered HIF-PH inhibitor that promotes erythropoiesis through increasing endogenous
production of erythropoietin, as well as improving iron regulation and overcoming the EPO-suppressive effects of inflammation on hemoglobin synthesis and red blood cell production by downregulating hepcidin.

Mechanism of Action:
Roxadustat is an orally bioavailable, hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), with potential anti-anemic activity. Upon administration, roxadustat binds to and inhibits HIF-PH, an enzyme responsible for the degradation of transcription factors in the HIF family under normal oxygen conditions. This prevents HIF breakdown and
promotes HIF activity. Increased HIF activity leads to an increase in endogenous erythropoietin production, thereby enhancing erythropoiesis. It also reduces the expression of the peptide hormone hepcidin, improves iron availability, and
boosts hemoglobin levels. HIF regulates the expression of genes in response to reduced oxygen levels, including genes
required for erythropoiesis and iron metabolism.
Administration of roxadustat has been shown to induce coordinated erythropoiesis, increasing red blood cell count while
maintaining plasma erythropoietin levels within or near normal physiologic range, in multiple subpopulations of CKD patients, including in the presence of inflammation and without a need for supplemental intravenous iron.

Pharmacodynamics:
Roxadustat reversibly binds to and potently inhibits hypoxia-inducible factor (HIF) prolyl hydroxylase enzymes, reducing
HIF-α breakdown and promoting HIF transcriptional activity. Activation of the HIF pathway in this manner results in the
induction of target genes involved in erythropoiesis, such as those for EPO, EPO receptor, proteins promoting iron absorption, iron transport and haem synthesis. Roxadustat dose-dependently increased hemoglobin levels, significantly
reduced hepcidin levels and transiently increased endogenous EPO levels within or near physiological range in patients with
anemia of CKD who were not dialysis dependent. Roxadustat reduced the dysregulation of iron metabolism associated with
CKD by increasing serum transferrin, intestinal iron absorption and the release of stored iron in a dose-dependent manner in
patients with anemia associated with dialysis dependent or dialysis-independent CKD. Cholesterol levels are also significantly
reduced from baseline with roxadustat, regardless of the use of statins or other lipid-lowering agents.

Indication:
Oroxat™ is indicated for the treatment of adult patients with symptomatic anemia associated with chronic kidney disease
(CKD).
Dosage & Administration:
Dosage
The appropriate dose of **Oroxat**™ must be taken orally three times per week and not on consecutive days. The dose should
be individualized to achieve and maintain target hemoglobin levels of 10 to 12 g/dL as described below:

- Patients not on erythropoiesis-stimulating agent treatment: For adults, the usual starting dose is 50 mg three times

weekly. The recommended starting dose of **Oroxat**™ 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 switching from erythropoiesis-stimulating agents: For adults, the usual starting dose is 70 or 100 mg three times

weekly. The dosage thereafter should be adjusted according to the patient's condition.

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

Oroxat™ treatment should not be continued beyond 24 weeks of therapy if a clinically meaningful increase in hemoglobin
levels is not achieved.

Dose Adjustment: When dose adjustments are required, increase or decrease the dose according to the "Dose increase/decrease table" and "Stepwise dose adjustment sequence" below.

Once adjusted, maintain the dose level for ≥4 weeks. If the hemoglobin concentration increases rapidly (>2.0 g/dL) within 4
weeks of a dose increase, decrease the dose or suspend the treatment immediately.

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).

Dose Increase/Decrease Table:

Change in Hemoglobin over the previous 4 weeks	Current Hemoglobin 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 Hemoglobin level and resume dosing when Hemoglobin 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	
Change in value of more than 2.0 g/dL	Decrease by 1 step			

Missed Dose: When there is ≥ 24-hour interval until the next scheduled dosing time, take the missed dose immediately and
follow the prescribed schedule for subsequent doses. If there is <24 hours until the next scheduled dosing time, skip the
missed dose, and take the next dose as scheduled. Do not take 2 doses on the same day.

Method of Administration: Oroxat™ tablets are to be taken orally with or without food.

Warnings & Precautions:

- It may initiate few thrombotic vascular events (TVEs) particularly in patients with pre-existing risk factors for TVE, including obesity and prior history of TVEs.
- Roxadustat should be used with caution in patients with a history of seizures.
- Roxadustat should not be administered if the patient has serious signs and symptoms of an infection. Roxadustat should

not be administered if the patient has liver disorder.

- Roxadustat should not be initiated in pregnant women.

Drug Interaction:
Roxadustat in combination with other medications may have drug-drug interaction.

Drug Used in Combination	Risk	Recommendation
Roxadustat with phosphate binders and other products containing multivalent cation EXCEPT lanthanum carbonate	Decreased roxadustat AUC by 67% and 46% and C_{max} by 66% and 52%	Roxadustat should be taken at least 1 hour after administration of phosphate binders or other medicinal products or supplements containing multivalent cations
Roxadustat with gemfibrozil (CYP2C8 and OATP1B1 inhibitor) or probenecid (UGT and OAT1/OAT3 inhibitor)	Increased roxadustat AUC by 2.3- fold and C_{max} by 1.4-fold	Adjust the dose of roxadustat following dose adjustment rules based on hemoglobin monitoring.
Roxadustat with OATP1B1 or BCRP substrates (simvastatin, rosuvastatin & atorvastatin)	AUC and C_{max} increased	Adjust the dose of roxadustat following dose adjustment rules based on hemoglobin monitoring.

Adverse Effects:
The common adverse reactions associated with roxadustat are hypertension, vascular access thrombosis, diarrhoea, peripheral oedema, hyperkalaemia and nausea.

Use in Special Populations:
Pregnant Women: There are no data on the use of Roxadustat in pregnant woman. Studies in animals have shown reproductive toxicity.
Roxadustat is contraindicated during the third trimester of pregnancy.
Roxadustat is not recommended during the first and second trimester of pregnancy.
If pregnancy occurs while Roxadustat is being administered, treatment should be discontinued and switched to alternative treatments, if appropriate.
Nursing Mothers: Roxadustat is contraindicated during breast-feeding.
Children: Roxadustat is not indicated in children.
Liver dysfunction patients: Roxadustat is not recommended for use in patients with severe hepatic impairment.

Overdose
Symptoms: When this drug was administered 5 mg/kg (510 mg) to a single healthy adult, increased heart rate transient have been reported. Hemoglobin concentration by overdosage of this drug is likely to increase more than necessary.
Treatment: Appropriate measures of dose reduction or interruption, etc. of this drug. This drug is not removed by dialysis.

Storage Conditions: Do not store above 30° C temperature. Keep away from light and wet place. Keep out of reach of children.

Packaging:
Oroxat™ 20 Tablet: Box containing 1 strip of 3 tablets. Each tablet contains Roxadustat INN 20 mg.
Oroxat™ 50 Tablet: Box containing 1 strip of 3 tablets. Each tablet contains Roxadustat INN 50 mg.
Oroxat™ 100 Tablet: Box containing 1 strip of 3 tablets. Each tablet contains Roxadustat INN 100 mg.

SK+F
Manufactured by
ESKAYEF PHARMACEUTICALS LTD.
TONGI, GAZIPUR, BANGLADESH
TM TRADEMARK
PM08740 V01