

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.

Drug-Drug Interactions

Based on in vitro data, roxadustat is an inhibitor of CYP2C8, BCRP, OATP1B1 and OAT3. 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.

Precautions for use

Misuse may lead to an excessive increase in packed cell volume. This may be associated with life-threatening complications of the cardiovascular system.

HOW SUPPLIED

Roxadustat (roxadustat) 20mg tablets are available in blister pack of 10's, 20's & 30's. Roxadustat (roxadustat) 50mg tablets are available in blister pack of 10's, 20's & 30's. Roxadustat (roxadustat) 70mg tablets are available in blister pack of 10's, 20's & 30's. Roxadustat (roxadustat) 100mg tablets are available in blister pack of 10's, 20's & 30's. Roxadustat (roxadustat) 150mg tablets are available in blister pack of 10's, 20's & 30's.

KEEP OUT OF REACH OF CHILDREN.

To be sold on prescription of a registered medical practitioner only.

INCOMPATIBILITIES:

Not applicable

SHELF LIFE:

2 years

SPECIAL PRECAUTIONS FOR STORAGE:

- Store below 30°C.
- Keep out of reach of children.
- Store away from direct sunlight, heat and moisture.
- To be sold on prescription of a registered medical practitioner only.

SPECIAL PRECAUTIONS FOR DISPOSAL:

No special requirements

Manufactured by:

Kaizen Pharmaceuticals (Pvt.) Ltd.
E-127/129, North Western Industrial Zone,
Bin Qasim, Karachi-75020, Pakistan.

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Roxadustat

(ROXADUSTAT)

20mg, 50mg, 70mg, 100mg
& 150mg Tablets

COMPOSITION**Roxadustat 20mg film-coated tablets**

Each film coated tablet contains:

Roxadustat..... 20mg

Roxadustat 50mg film-coated tablets

Each film coated tablet contains:

Roxadustat..... 50mg

Roxadustat 70mg film-coated tablets

Each film coated tablet contains:

Roxadustat..... 70mg

Roxadustat 100mg film-coated tablets

Each film coated tablet contains:

Roxadustat..... 100mg

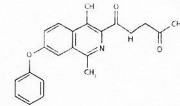
Roxadustat 150mg film-coated tablets

Each film coated tablet contains:

Roxadustat..... 150mg

DESCRIPTION

Roxadustat is a first-in-class hypoxia-inducible factor prolyl hydroxylase inhibitor used to treat anemia associated with chronic kidney disease. It works by reducing the breakdown of the hypoxia-inducible factor (HIF), which is a transcription factor that stimulates red blood cell production in response to low oxygen levels. The chemical formula is C₁₉H₁₆N₂O₅. Its structural formula is:

**INDICATED**

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

POSOLGY 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 Roxadustat, 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.

POSOLGY

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

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Product: Roxadustat Tablets Leaflet
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Artwork created on: March 25, 2024



DEPARTMENT	SIGNATURE	DATE / TIME	REMARKS
Marketing			
Regulatory		26-03-2025	OK
Quality Assurance		26/03/25	OK
Quality Control		26/03/25	only LG reviewed
Production		26/03/25	OK

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 70mg three times per week in patients weighing less than 100 kg and 100mg 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.

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. The first roxadustat dose should replace the next scheduled dose of the current ESA.

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 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.

CONTRAINDICATED

Roxadustat is contraindicated in the following conditions:
• Hypersensitivity to the active substance, peanut, soya.
• Third trimester of pregnancy
• Breast-feeding

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.
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.

BREAST FEEDING

It is unknown whether roxadustat/metabolites are excreted in human milk. Available animal data have shown excretion of roxadustat in milk.
Roxadustat is contraindicated during breast-feeding.

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. Women of childbearing potential must use highly effective contraception during treatment and for at least one week after the last dose of Roxadustat.

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 Roxadustat. Therefore, caution should be exercised when driving or using machines.

PHARMACOLOGICAL PROPERTIES:

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 adaptive 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.

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.

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.

Bioluminescence

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.

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Production	<i>[Signature]</i>	26/03/25	OK

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