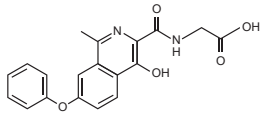
Roxaget™

(R o x a d u s t a t)

روکزاگیٹ

Film-coated Tablets
20mg, 50mg & 100mg

DESCRIPTION
Roxaget Tablets contains Roxadustat, a first orally administered hypoxia-inducible factor (HIF) prolyl hydroxylase (PH) inhibitor. The chemical name of Roxadustat is [(4-hydroxy-1-methyl-7-phenoxyisoquinoline-3-carbonyl) amino] acetic acid. Its molecular formula is $C_{19}H_{16}N_2O_5$ and the structural formula is:



Roxadustat

QUALITATIVE & QUANTITATIVE COMPOSITION
Roxaget (Roxadustat) Tablets are available for oral administration as:

Roxaget Tablets 20mg
Each film-coated tablet contains:
Roxadustat…20mg

Roxaget Tablets 50mg
Each film-coated tablet contains:
Roxadustat…50mg

Roxaget Tablets 100mg
Each film-coated tablet contains:
Roxadustat…100mg

CLINICAL PHARMACOLOGY
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 24L.

Metabolism
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.

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 1.1L/h in patients with CKD not on dialysis and 1.4L/h in patients with CKD on dialysis. Roxadustat and its metabolites are not significantly removed by haemodialysis. When radiolabeled 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 Population
Hepatic and Renal Impairment
Following a single dose of 100mg 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.

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

DOSAGE & ADMINISTRATION
Treatment with Roxaget (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 Roxaget (Roxadustat) Tablets, 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.

General Considerations
The appropriate dose of Roxaget (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 12g/dL as described below.

Roxaget (Roxadustat) treatment should not be continued beyond 24 weeks of therapy if a clinically meaningful increase in Hb levels is not achieved. Alternative explanations for an inadequate response should be sought and treated before re-starting Roxaget Tablets.

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 Roxaget (Roxadustat) is 70mg three times per week in patients weighing less than 100kg and 100mg three times per week in patients weighing 100kg and over.

Patients converting from an ESA
Patients currently treated with an ESA can be converted to Roxaget (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 Roxaget (Roxadustat) should be based on a benefit-risk consideration for the individual patient.
The recommended starting dose of Roxaget (Roxadustat) is based on the average prescribed ESA dose in the 4 weeks before conversion. The first Roxaget (Roxadustat) dose should replace the next scheduled dose of the current ESA.

Starting doses of Roxadustat to be taken three times per week by patients switching from an ESA

Darbepoetin alfa intravenous or subcutaneous dose (micrograms/week)	Epoetin intravenous or subcutaneous dose (IU/week)	Methoxy-polyethyleneglycol-epoetin beta intravenous or subcutaneous dose (micrograms/month)	Roxadusat dose (mg 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	More than 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

ESL: erythropoiesis-stimulating drug

Dose adjustment and Hb monitoring
The individualized maintenance dose ranges from 20mg to 400mg three times weekly. Hb values should be monitored every two weeks until the desired Hb value of 10 to 12g/dL is reached and stabilised, and every four weeks thereafter, or as clinically indicated.

The dose of Roxadustat may be adjusted incrementally up or down from the starting dose 4 weeks after the start of treatment, and every 4 weeks thereafter unless Hb increases by more than 2g/dL, in which case dose should be immediately reduced by one step. When adjusting the dose of Roxadustat, the current Hb value and the rate of change in the Hb value over the past 4 weeks should be taken into account and the dose adjustment steps based on the dose adjustment schedule in Table below should be followed.

Incremental dose adjustments up or down should follow the order of available doses: 20mg to 40mg to 50mg to 70mg to 100mg to 150mg to 200mg to 250mg to 300mg to 400mg (for chronic kidney disease patients on dialysis only).

Dose adjustment schedule

Change in Hb in the last 4 weeks*	Current Hb value (g/dL):			
	Under 10.5	10.5 to 11.9	12.0 to 12.9	13.0 or above
Change in value of more than +1.0g/dL	No change	Reduce the dose by one step	Reduce the dose one step	Withhold dosing, monitor Hb level and resume dosing when Hb is less than 12.0g/dL, at a dose that is reduced by two steps.
Change in value between -1.0 and +1.0g/dL	Increase the dose by one step	No change	Reduce the dose by one step	
Change in value of less than -1.0g/dL	Increase the dose by one step	Increase the 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 2g/dL at any time within a 4-week period, in which case dose should be immediately reduced by one step.
*Change in haemoglobin (Hb) in the last 4 weeks = (current Hb value) – (previous Hb value measured 4 weeks earlier).

If further dose reduction is required for a patient who is already on the lowest dose (20mg three times weekly), dose of 20mg should not be reduced by dividing the tablet, but the dose frequency should be reduced to twice weekly. If further dose reduction is needed, the dose frequency may be reduced further, to once a week.

Maintenance dose
After stabilisation of Hb to the target value of between 10 and 12g/dL, Hb should continue to be monitored regularly and the dose adjustment schedule should be followed.

Patients starting dialysis while being treated with Roxadustat
No specific dose adjustment is required in patients with chronic kidney disease who start dialysis during treatment with Roxadustat. The normal dose adjustment schedule should be followed.

Concomitant use of Roxadustat with inducers or inhibitors
When concomitant treatment with strong inhibitors (e.g. gemfibrozil) or inducers (e.g. rifampicin) of CYP2C8, or inhibitors (e.g. probenecid) of UGT1A9 is initiated, Hb should be routinely monitored and the dose adjustment schedule should be followed.

Maximum recommended dose
Patients not on dialysis should not exceed a Roxadustat dose of 3mg/kg body weight or 300mg three times weekly, whichever is lower.

Patients on dialysis should not exceed a Roxadustat dose of 3mg/kg body weight or 400mg 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 should be taken as soon as possible. If there is 1 day or less until the next scheduled dose, the missed dose should be skipped, and the next dose should be taken on the next scheduled day. In both cases, the regular dosing schedule should be resumed thereafter.

Special Population
Elderly
No adjustment of the starting dose is required for elderly patients.

Patients with Hepatic Impairment
No adjustment of the starting dose 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). Roxaget (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.

Pediatric Population
Safety and efficacy of Roxadustat in pediatric patients under 18 years of age have not been established.

Method of Administration
Roxaget (Roxadustat) Tablets are to be taken orally with or without food. Roxaget (Roxadustat) 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 photo degradation. 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.

ADVERSE REACTIONS
Following adverse reactions have been reported with the use of Roxadustat:

Very Common
Hyperkalaemia, hypertension, vascular access thrombosis (VAT), nausea, diarrhea and peripheral oedema.

Common
Sepsis, insomnia, seizures, headache, deep vein thrombosis (DVT), constipation and vomiting.

Uncommon
Hyperbilirubinaemia and pulmonary embolism.

Not Known
Secondary hypothyroidism, dermatitis exfoliative generalised (DEG) and blood thyroid stimulating hormone (TSH) decreased.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363."

CONTRAINDICATIONS
Roxadustat is contraindicated in:
- Patients with hypersensitivity to the active substance, peanut, soya or to any of the excipient of the product.
- Third trimester of pregnancy.
- Breast-feeding.

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. In the case of non-responsiveness, treatment with Roxadustat should not be continued beyond 24 weeks after the start of treatment. Conversion of dialysis patients otherwise stable on ESA treatment is only to be considered when there is a valid clinical reason. For stable ESA treated patients with anaemia associated with CKD and not on dialysis, this risk could not be estimated as these patients have not been studied. A decision to treat these patients with Roxadustat should be based on a benefit risk consideration for the individual patient.

Thrombotic vascular events (TVEs)
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]). Deep vein thrombosis was reported as common and pulmonary embolism as uncommon amongst the patients in clinical studies. The majority of DVT and PE events were serious. Vascular access thrombosis (VAT) was reported as very common amongst the CKD patients on dialysis in clinical studies. 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
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 with the use of Roxadustat. 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, haemolysis, severe aluminium toxicity, underlying haematologic 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 Tablets should not be continued beyond 24 weeks of therapy.

Hepatic impairment
Caution is warranted when Roxadustat is administered to 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).

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

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

Excipients
Roxadustat Tablets contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Pregnancy
Roxadustat is contraindicated during the third trimester of pregnancy. Roxadustat is not recommended during the first and second trimester of pregnancy. Roxadustat should not be initiated in women planning on becoming pregnant, during pregnancy or when anaemia associated with CKD is diagnosed during pregnancy. In such cases, alternative therapy should be started, if appropriate. 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.

Nursing Mothers
Roxadustat Tablets are contraindicated during breast-feeding.

DRUG INTERACTIONS
Effect of other medicinal products on Roxadustat
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 containing calcium, iron, magnesium or aluminium. 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.

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 based on Hb monitoring.

Effects of Roxadustat on other medicinal products.
OATP1B1 or BCRP Substrates
Interactions are expected with 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 may increase the plasma exposure of other medicinal products that are substrates of BCRP or OATP1B1. Monitor for possible adverse reactions of co-administered medicinal products and adjust dose accordingly.

Roxadustat and erythropoiesis-stimulating agents (ESAs)
It is not recommended to combine administration of Roxadustat and ESAs as the combination has not been studied.

OVERDOSAGE
Single supratherapeutic doses of Roxadustat 5mg/kg (up to 510mg) 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. Roxadustat overdose can elevate Hb levels above the desired level (10-12g/dL), which should be managed with discontinuation or reduction of Roxadustat dosage and careful monitoring and treatment as clinically indicated. Roxadustat and its metabolites are not significantly removed by haemodialysis.

STORAGE
Do not store above 30°C.
Protect from sunlight & moisture.

The expiration date refers to the product correctly stored at the recommended conditions.

HOW SUPPLIED
Roxaget (Roxadustat) Tablets 20mg are available in pack of 12's.
Roxaget (Roxadustat) Tablets 50mg are available in pack of 12's.
Roxaget (Roxadustat) Tablets 100mg are available in pack of 12's.

Keep out of reach of children.

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

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
Getz pharma (PVT) LIMITED
www.getzpharma.com
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