

Daprostat™ (Daprodustat)

ڈاپرو سٹاٹ

COMPOSITION:

Daprostat Tablet 2 mg:

Each film coated tablet contains:
Daprodustat 2 mg.

Product Specs.: Innovator

Daprostat Tablet 4 mg:

Each film coated tablet contains:
Daprodustat 4 mg.

Product Specs.: Innovator

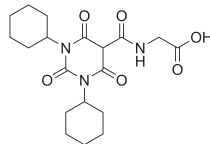
Daprostat Tablet 6 mg:

Each film coated tablet contains:
Daprodustat 6 mg.

Product Specs.: Innovator

DESCRIPTION:

Daprostat contains daprodustat, an inhibitor of hypoxia inducible factor (HIF), prolyl 4- hydroxylases (PH1, PH2 and PH3). The chemical name of daprodustat is N-((1,3-dicyclohexyl)hexahydro-2,4,6-trioxypyrimidin-5-yl) carbonyl]glycine. The molecular formula of daprodustat is C₂₆H₄₂N₂O₆ and its molecular mass is 393.43. The structural formula is shown below



CLINICAL PHARMACOLOGY:

Pharmacotherapeutic group: Anti-anemic preparations, other anti-anemic preparations.

ATC code: B03XA07

Mechanism of Action: Daprodustat is a reversible inhibitor of HIF-PH1, PH2 and PH3 (IC50 in the low nM range). This activity results in the stabilization and nuclear accumulation of HIF-1α and HIF-2α transcription factors, leading to increased transcription of the HIF-responsive genes, including erythropoietin.

Pharmacokinetics:

Absorption: Following oral administration, daprodustat is rapidly absorbed (T_{max}: 1–4 hours) with 65% absolute bioavailability. A high-fat, high-calorie meal does not significantly affect its exposure.

Distribution: Daprodustat distributes almost equally between plasma and blood cells (blood:plasma ratio 1.23), with a steady-state volume of distribution of 14.3 L. It is >99% bound to plasma proteins in vitro.

Metabolism: Daprodustat is primarily metabolized by CYP2C8 (95%) and to a lesser extent by CYP3A4 (5%). About 40% of circulating plasma radioactivity is from the parent drug; the rest is from metabolites. Three major metabolites (>10% each) have been identified, which may contribute to pharmacologic effects, though their exact role is unknown.

Excretion: Daprodustat has a mean plasma clearance of 18.9 L/h (hepatic extraction ~18%). Within 7 days of dosing, 74% of radioactivity is recovered in feces and 21% in urine, with ~99.5% excreted as oxidative metabolites.

Special populations:

Elderly: Age (22–93 years) does not significantly affect daprodustat pharmacokinetics.

Renal Impairment: Daprodustat exposure is similar across renal function levels and is not significantly affected by dialysis. However, metabolite exposure increases with CKD severity and is higher on non-dialysis days.

Hepatic Impairment: In mild to moderate hepatic impairment, daprodustat exposure increases up to 2.3-fold. Effects in severe hepatic impairment are unknown, as it has not been studied in this population.

INDICATIONS:

Daprodustat is indicated for the treatment of anemia due to chronic kidney disease (CKD) in adults who have been receiving dialysis for at least four months.

It is not indicated for use:

- As a substitute for red blood cell transfusions in patients who require immediate correction of anemia.
- For treatment of anemia of chronic kidney disease in patients who are not on dialysis.

DOSAGE & ADMINISTRATION:

Individualize dosing and use the lowest dose of Daprodustat sufficient to reduce the need for red blood cell transfusions. Do not target a hemoglobin higher than 11 g/dL. It can be taken with or without food, and without regard to concomitant administration of iron or phosphate binders. It should be swallowed whole. Tablets should not be cut, crushed, or chewed. Daprodustat can be administered without regard to the timing or type of dialysis. If a dose of Daprodustat is missed, it should be taken as soon as possible, unless it is the same day as the next dose. In this case, the missed dose should be skipped, and the next dose taken at the usual time. Double-doses should not be taken to make-up for a missed dose.

CONTRAINDICATIONS:

- Patients receiving a strong CYP2C8 inhibitor such as gemfibrozil.
- Patients with uncontrolled hypertension

WARNINGS AND PRECAUTIONS:

Thrombotic Events & Mortality:

Daprodustat increases the risk of arterial and venous thrombotic events (e.g., MI, stroke, VTE, vascular access thrombosis), which may be fatal. Risk is higher in patients with recent cardiovascular or cerebrovascular events (within 3 months). Avoid targeting Hb >11 g/dL or rapid Hb rises (>1 g/dL in 2 weeks), as this may further increase risks. Use the lowest effective dose to reduce transfusion needs.

Heart Failure Risk:

In the ASCEND-D trial, heart failure hospitalizations were more common in patients with pre-existing heart failure receiving Daprodustat versus rEPO. Monitor closely and educate patients on symptoms.

Hypertension:

Contraindicated in uncontrolled hypertension. Worsening hypertension (including hypertensive crisis and seizures) was observed. Regularly monitor BP and manage appropriately.

Gastrointestinal Erosions:

GI erosions and bleeding occurred in patients on Daprodustat, especially in those with predisposing factors (e.g., PUD, alcohol, smoking, NSAID use). Counsel patients on symptoms and seek timely medical care if needed.

Not Recommended in CKD Patients Not on Dialysis:

In the ASCEND-ND trial, non-dialysis CKD patients showed increased risk of CV death, stroke, AKI, HF hospitalization, and GI complications. Use in this group is not recommended.

Malignancy Risk:

Daprodustat is not recommended in patients with active cancer due to potential HIF-1 mediated effects, though no increased carcinogenicity was seen in animals.

DRUG INTERACTIONS:

- **CYP2C8 Inhibitors:** Concomitant administration of strong CYP2C8 inhibitors (e.g., gemfibrozil) with Daprodustat is contraindicated due to a marked increase in Daprodustat exposure. Concomitant administration of moderate CYP2C8 inhibitors (e.g., clopidogrel) increases Daprodustat exposure. Reduce the starting dose of Daprodustat by half when initiating treatment in patients on clopidogrel or a moderate CYP2C8 inhibitor except in patients whose starting dose is already 1 mg. Monitor hemoglobin and adjust the dose of Daprodustat when initiating or stopping therapy with clopidogrel or a moderate CYP2C8 inhibitor during treatment with Daprodustat.
- **CYP2C8 Inducers:** CYP2C8 inducers (e.g., rifampin) may decrease Daprodustat exposure, which may result in loss of efficacy. Monitor hemoglobin and adjust the dose of Daprodustat when initiating or stopping therapy with CYP2C8 inducers during treatment with Daprodustat.

USE IN SPECIFIC POPULATION:

Pregnancy:

Limited human data; potential fetal risk cannot be ruled out. Animal studies showed fetal loss and reduced weight at doses causing maternal toxicity. Advise pregnant women of potential risks.

Breastfeeding:

Unknown if daprodustat is present in human milk, but detected in rat milk. Due to potential serious adverse effects, breastfeeding is not recommended during treatment and for one week after the last dose.

Fertility:

In rats, high doses caused reduced fertility and fetal viability, linked to maternal toxicity and polycythemia.

ADVERSE REACTIONS:

- Increased Risk of Death, Myocardial Infarction, Stroke, Venous Thromboembolism, and Thrombosis of Vascular Access.
- Risk of Hospitalization for Heart Failure.
- Hypertension.
- Gastrointestinal Erosion.

OVERDOSE:

Headache and gastrointestinal adverse reactions (e.g., nausea) may be seen with acute overdose with Daprodustat. There is no specific antidote. Hemodialysis will not substantially remove Daprodustat because it is highly protein bound.

INSTRUCTIONS:

- Store below 30°C.
- 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:

- Daprostat Tablet 2 mg** : Pack of 3 x 10 tablets.
- Daprostat Tablet 4 mg** : Pack of 3 x 10 tablets.
- Daprostat Tablet 6 mg** : Pack of 3 x 10 tablets.

FOR FURTHER INFORMATION PLEASE CONTACT:



Manufactured by:
CCL Pharmaceuticals (Pvt.) Ltd.
62 Industrial Estate, Kot Lakhpat, Lahore, Pakistan.

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 نسخے پر فروخت کریں۔