Daprodu™

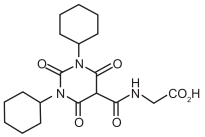
(D a p r o d u s t a t)

ڈیپروڈو

Film Coated Tablets 1mg, 2mg, 4mg & 6mg

DESCRIPTION

Daprodustat is an inhibitor of hypoxia inducible factor (HIF), prolyl 4- hydroxylases (PH)1, PH2 and PH3. The chemical name of Daprodustat is N-[(1,3-dicyclohexylhexahydro-2,4,6-trioxopyrimidin-5-yl) carbonyl]glycine. Its molecular formula is $C_{19}H_{27}N_3O_6$ and the structural formula is:



Daprodustat

QUALITATIVE & QUANTITATIVE COMPOSITION

Daprodu (Daprodustat) is available for oral administration as:

Daprodu Tablets 1mg
Each film-coated tablet contains:
Daprodustat …1mg

Daprodu Tablets 2mg
Each film-coated tablet contains:
Daprodustat …2mg

Daprodu Tablets 4mg
Each film-coated tablet contains:
Daprodustat …4mg

Daprodu Tablets 6mg
Each film-coated tablet contains:
Daprodustat …6mg

CLINICAL PHARMACOLOGY

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

Daprodustat exposure generally increases in a dose-proportional manner over the range of approved doses. Steady-state concentrations are achieved within 24-hours of dosing.

Absorption

Following oral administration, Daprodustat is readily absorbed with median time to peak concentration (T_{max}) in healthy subjects ranging from 1 hour to 4 hours. The absolute bioavailability of Daprodustat is 65%. Administration of Daprodustat with a high fat/high calorie meal did not significantly alter Daprodustat exposure compared to administration in the fasted state.

Distribution

Daprodustat has an approximately equal distribution between plasma and blood cells (blood:plasma ratio of 1.23). Following intravenous dosing, the volume of distribution at steady-state in healthy subjects is 14.3L. In vitro, plasma protein binding of Daprodustat is >99%.

Metabolism

In vitro, Daprodustat is primarily metabolized by CYP2C8 (95% contribution), with a minor contribution by CYP3A4 (5%). Following oral or intravenous administration of radiolabeled Daprodustat to healthy adults, approximately 40% of the total circulating radioactivity in plasma was Daprodustat, and the remaining 60% was metabolites.

Elimination

The terminal elimination half-life of Daprodustat is approximately 1 hour to 4 hours. Mean clearance from plasma was 18.9L/h, which correlates to blood clearance of 15L/h and equates to a hepatic extraction of approximately 18%.

Special Populations

Patients with Renal Impairment

The steady-state exposure of Daprodustat is similar in patients with normal renal function and those with varying degrees of renal impairment; Daprodustat exposure is not significantly impacted by hemodialysis or peritoneal dialysis. The systemic exposure of Daprodustat metabolites was higher in patients with Stage 3 to 5 CKD compared to those with normal renal function. Exposures of metabolites were higher on non-dialysis days compared to dialysis days.

Patients with Hepatic Impairment

Following administration of a single Daprodustat 6mg dose, mean Daprodustat C_{max} and AUC increased by 2-fold and unbound exposure increased by 2.3-fold in subjects with moderate hepatic impairment (Child-Pugh Class B) compared to subjects with normal hepatic and renal function. For those with mild hepatic impairment (Child-Pugh Class A), mean Daprodustat C_{max} was similar while AUC increased by 1.5-fold and unbound C_{max} and AUC increased by 1.6 and 2.2-fold, respectively, compared to subjects with normal hepatic and renal function. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of Daprodustat is unknown.

THERAPEUTIC INDICATIONS

Daprodu (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.

Limitations of Use

Daprodu (Daprodustat) 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 AND ADMINISTRATION

Important Dosing Information

- Individualize dosing and use the lowest dose of Daprodu (Daprodustat) tablets sufficient to reduce the need for red blood cell transfusions.
- Do not target a hemoglobin higher than 11g/dL.
- Daprodu (Daprodustat) tablets can be taken with or without food, and without regard to concomitant administration of iron or phosphate binders.
- Daprodu (Daprodustat) tablets should be swallowed whole. Tablets should not be cut, crushed, or chewed.
- Daprodu (Daprodustat) tablets can be administered without regard to the timing or type of dialysis.
- If a dose of Daprodu (Daprodustat) tablets 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.

Recommended Starting Dose of Daprodustat

Adults with Anemia Due to Chronic Kidney Disease Receiving Dialysis for at Least 4 Months

Adults Not Being Treated with an ESA (Erythropoiesis Stimulating Agent)

For adults not being treated with an ESA, the starting dose of Daprodu (Daprodustat) tablets is based on the hemoglobin level see Table below. Dose modifications are needed for patients receiving concomitant treatment with a moderate CYP2C8 inhibitor or moderate hepatic impairment.

Table 1: Starting Dose of Daprodu (Daprodustat) for Adults on Dialysis not receiving an ESA

Pre-Treatment Hemoglobin Level (g/dL)	Starting Dose of Daprodustat (Once Daily Dosing)[a]
<9	4mg
≥9 to ≤10	2mg
>10	1mg

[a]See dosing modification if the patient has moderate hepatic impairment and if the patients is on a moderate CYP2C8 inhibitor.

Adults Being Switched from an ESA (Erythropoiesis Stimulating Agent)

For adults being switched from an ESA to Daprodu (Daprodustat), the starting dose of Daprodu (Daprodustat) is based on the dose regimen of the ESA at the time of substitution. Dose modifications are needed for patients receiving concomitant treatment with a moderate CYP2C8 inhibitor or moderate hepatic impairment.

Table 2: Starting Dose of Daprodu (Daprodustat) for Adults on Dialysis Switching from an ESA

Current Dose of ESA			Dose of Daprodustat[a]
Epoetin Alfa[b] Intravenous (units/week)	Darbepoetin Alfa Subcutaneous /Intravenous (mcg/4 weeks)	Methoxy PEG-Epoetin Beta Subcutaneous /Intravenous (mcg/month)	Once Daily Dosing
Less than or equal to 2,000	20 to 30	30 to 40	4mg
Greater than 2,000 to less than 10,000	Greater than 30 to 150	Greater than 40 to 180	6mg
Greater than or equal to 10,000 to less than 20,000	Greater than 150 to 300	Greater than 180 to 360	8mg
Greater than or equal to 20,000	Greater than 300	Greater than 360	12mg

[a]See dosing modifications, if the patient has moderate hepatic impairment and if the patient is on a moderate CYP2C8 inhibitor.

[b]For patients on subcutaneous epoetin alfa, convert the epoetin alfa subcutaneous dose to intravenous dose equivalent by multiplying the subcutaneous dose received per week by 1.42 to obtain the weekly intravenous dose.

Monitoring Response to Therapy and Dose Adjustment

Following initiation of therapy and after each dose adjustment, monitor hemoglobin every 2 weeks for the first month and then every 4 weeks thereafter.

When adjusting doses of Daprodu (Daprodustat) tablets, consider hemoglobin rate of rise, rate of decline and hemoglobin variability. Do not increase the dose of Daprodu (Daprodustat) more frequently than once every 4 weeks.

- If the dose of Daprodu (Daprodustat) needs to be adjusted, increase or decrease by one dose level at a time (see Table 3).
- Decrease the dose of Daprodu (Daprodustat) if hemoglobin increases rapidly (e.g., greater than 1g/dL over 2 weeks or greater than 2g/dL over 4 weeks) or if the hemoglobin exceeds 11g/dL.
- If hemoglobin exceeds 12g/dL, interrupt treatment with Daprodu (Daprodustat) tablets. When the hemoglobin is within the target range, treatment may be restarted at one dose level lower (see Table 3).
- Treatment with Daprodu (Daprodustat) tablets should not be continued beyond 24 weeks of therapy if a clinically meaningful increase in hemoglobin level is not achieved. Alternative explanations for an inadequate response should be sought and treated before re-starting therapy.

Table 3:Dose Levels of Daprodustat

Daily dose of Daprodustat	1mg	2mg	4mg	6mg	8mg	12mg	16mg	24mg[a]

[a] 24mg is the maximum recommended once daily dose.

Dosage Modification for Hepatic Impairment

Reduce the starting dose of Daprodu (Daprodustat) tablets by half (see Tables 1 and 2) in patients with moderate hepatic impairment (Child-Pugh Class B) except in patients

whose starting dose is already 1mg.
Use of Daprodu (Daprodustat) in patients with severe hepatic impairment (Child-Pugh Class C) is not recommended.

Dosage Modification for Concomitant Treatment with Moderate CYP2C8 Inhibitors
Reduce the starting dose of Daprodu (Daprodustat) by half (see table 1 and 2) in patients who are on clopidogrel or a moderate CYP2C8 inhibitor except in patients whose starting dose is already 1mg.
Monitor hemoglobin and adjust the dose of Daprodu (Daprodustat) when initiating or stopping therapy with clopidogrel or a moderate CYP2C8 inhibitor during treatment with Daprodu (Daprodustat).

ADVERSE REACTIONS
Following adverse reaction have been reported with the use of Daprodustat:
Increased risk of death, myocardial Infarction, stroke, venous thromboembolism, and thrombosis of vascular access, risk of hospitalization for heart failure, hypertension, gastrointestinal erosion, retinal hemorrhage, hypersensitivity (rash, dermatitis, urticaria), stomach ache, constipation and peripheral edema.

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

CONTRAINDICATIONS
Daprodustat is contraindicated in patients:
- With hypersensitivity to the active substance or to any of the excipients of the product.
- Receiving a strong CYP2C8 inhibitor such as gemfibrozil.
- With uncontrolled hypertension.

PRECAUTIONS

WARNING: INCREASED RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, and THROMBOSIS OF VASCULAR ACCESS
Daprodustat increases the risk of thrombotic vascular events, including Major Adverse Cardiovascular Events (MACE). Targeting a hemoglobin level greater than 11 g/dL is expected to further increase the risk of death and arterial venous thrombotic events, as occurs with Erythropoietin Stimulating Agents (ESAs), which also increase erythropoietin levels. Use the lowest dose of Daprodustat sufficient to reduce the need for red blood cell transfusions.

Increased Risk of Death, Myocardial Infarction, Stroke, Venous Thromboembolism, and Thrombosis of Vascular Access
Daprodustat increases the risk of arterial and venous thrombotic events that may be fatal, including myocardial infarction, stroke, venous thromboembolism and vascular access thrombosis.
Patients with cardiovascular or cerebrovascular disease are at increased risk of these events. Avoid use in patients with a history of myocardial infarction, cerebrovascular event, or acute coronary syndrome within the 3 months prior to starting Daprodustat.
Use the lowest dose of Daprodustat sufficient to reduce the need for red blood transfusions. Adherence to dosing and hemoglobin monitoring recommendations is important to avoid excessive erythropoiesis.
Advise patients to seek immediate medical attention if they develop signs or symptoms of myocardial infarction, stroke, venous thromboembolism, or thrombosis of vascular access. Evaluate and manage promptly if these occur.

Risk of Hospitalization for Heart Failure
Risk of hospitalization is increased in patients with a history of heart failure. Consider the patient's history of heart failure when deciding whether to prescribe Daprodustat. Advise patients of the symptoms and signs of heart failure and to immediately report any worsening to their healthcare provider.

Gastrointestinal Erosion
Serious erosions, including gastrointestinal bleeding and the need for red blood cell transfusions, were reported in 3.6% and 3.1% of those receiving Daprodustat and rhEPO (recombinant human erythropoietin), respectively. Consider this risk particularly in patients at increased risk for gastrointestinal erosions, such as those with a history of gastrointestinal erosion, peptic ulcer disease, use of concomitant medications that increase the risk of gastrointestinal erosion, and current tobacco smokers and alcohol drinkers.
Advice patients of the symptoms and signs of gastric and esophageal erosions and of gastrointestinal bleeding and to seek prompt medical care if these occur.

Serious Adverse Events in Patients with Anemia Due to Chronic Kidney Disease and Not on Dialysis
The safety of Daprodustat has not been established for the treatment of anemia due to CKD in adults not on dialysis and its use is not recommended in this setting.

Malignancy
Because increased hypoxia inducible factor (HIF)-1 levels may be associated with unfavorable effects on cancer growth, Daprodustat has not been studied and is not recommended in patients with active malignancies.

Hypertension
Daprodustat is contraindicated in patients with uncontrolled hypertension. Cases of hypertensive crisis including hypertensive encephalopathy and seizures have also been reported in patients receiving Daprodustat. Periodically monitor blood pressure and adjust or initiate anti-hypertensive therapy as needed.

Pregnancy
Daprodustat should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the fetus.

Nursing Mother
Advise females not to breastfeed during treatment with Daprodustat and for one week after the final dose.

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 1mg. 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.

OVERDOSAGE
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.

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

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

HOW SUPPLIED
Daprodu (Daprodustat) Tablets 1mg are available in blister pack of 30's.
Daprodu (Daprodustat) Tablets 2mg are available in blister pack of 30's.
Daprodu (Daprodustat) Tablets 4mg are available in blister pack of 30's.
Daprodu (Daprodustat) Tablets 6mg are available in blister pack of 30'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.

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