



# CPP / 13 Date 05-11-2025 Font Size 5 Size 216mmx 140mm

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## Cardiac Electrophysiology

At a dose 10 times the maximum recommended dose, daprodustat does not prolong the QTc interval to any clinically relevant extent.

## 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<sub>max</sub>) in healthy subjects ranging from 1 hour to 4 hours. The absolute bioavailability of daprodustat is 65%. Administration of Daprotab with a high fat/high caloric 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 14.3 L. In vitro, plasma protein binding of daprodustat is >99%.

## Elimination

The terminal elimination half-life of daprodustat is approximately 1 hour to 4 hours.

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.

Excretion: Mean clearance from plasma was 18.9 L/h, which correlates to blood clearance of 15 L/h and equates to a hepatic extraction of approximately 18%.

Within seven days of an oral dose of radiolabeled daprodustat, 74% of the radioactivity was recovered in the feces, and 21% in the urine. Approximately 99.5% of the dose was excreted as oxidative metabolites, with the rest accounted for by daprodustat.

## Specific Populations

Elderly: Population pharmacokinetic analyses in adults with CKD (22 years to 93 years) showed that age did not influence the pharmacokinetics of daprodustat.

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.

## Hepatic Impairment

Following administration of a single Daprotab 6 mg dose, mean daprodustat C<sub>max</sub> and AUC increased by 2-fold and unbound exposure increased by 2.3-fold in subjects with moderate hepatic impairment.

Mild hepatic impairment, for those with mild hepatic impairment (Child-Pugh Class A), mean daprodustat C<sub>max</sub> was similar while AUC increased by 1.5-fold and unbound C<sub>max</sub> and AUC increased by 1.6 and 2.2-fold, respectively, compared to subjects with normal hepatic and renal function.

Severe hepatic impairment, the effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of daprodustat is unknown as there have been no studies of Daprotab in patients with severe hepatic impairment.

## Drug Interaction Studies

Clinical Studies: Effect of CYP2C8 Inhibitors on the Pharmacokinetics of Daprodustat: The concomitant administration of gemfibrozil 600 mg twice a day for 5 days (strong CYP2C8 inhibitor) with a single 100 mg dose of Daprotab on Day 4 of gemfibrozil administration resulted in an 18.6-fold increase in AUC (0-∞) and a 3.9-fold increase in C<sub>max</sub> of daprodustat.

The concomitant administration of trimethoprim 200 mg twice a day for 5 days (CYP2C8 weak inhibitor) and 25 mg single dose of Daprotab on Day 4 of trimethoprim administration resulted in a 1.5-fold increase in AUC (0-∞) and a 1.3-fold increase in C<sub>max</sub> of daprodustat.

Daprodustat AUC and C<sub>max</sub> are expected to increase at least 4-fold and 3-fold, respectively, following concomitant administration of daprodustat with clopidogrel 75 mg once daily (moderate CYP2C8 inhibitor).

Following 4 weeks of Daprotab dosing, hemoglobin changes from baseline were similar in subjects with and without concomitant use of clopidogrel. Effect of Daprodustat on the Pharmacokinetics of Other Drugs: Clinical drug interaction studies showed that daprodustat inhibition of CYP2C8 and OATP1B1/OATP1B3 demonstrated

no clinically significant effect on pioglitazone (CYP2C8 substrate) or rosuvastatin (OATP1B1/OATP1B3 substrate) C<sub>max</sub> or AUC.

In vitro studies: Some oxidative metabolites of daprodustat are substrates of Organic Anion Transporter (OAT1) or OAT3; however, the clinical significance of this is unknown. Daprodustat is a substrate of Breast Cancer Resistance Protein (BCRP); however, the risk of significant drug interactions between daprodustat and BCRP inhibitors is considered low given the absorption and metabolism profile of daprodustat.

Daprodustat is not an inducer of CYP1A2, CYP2B6 and CYP3A4. Daprodustat is not an inhibitor of P-glycoprotein (P-gp) and BCRP.

Daprodustat is not a substrate of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and P-gp. The major metabolites are not substrates of OATP1B1, OATP1B3, OAT2B1, Organic Cation Transporter (OCT)1, OCT2, Multidrug and Toxin Extrusion (MATE)1 and MATE2-K.

## WARNINGS AND PRECAUTIONS

### Increased Risk of Death, Myocardial Infarction, Stroke, Venous Thromboembolism, and Thrombosis of Vascular Access

Daprotab 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 Daprotab.

A rate of hemoglobin rise of greater than 1 g/dL over 2 weeks may contribute to these risks. Targeting a hemoglobin level of greater than 11 g/dL is expected to further increase the risk of death and arterial and venous thrombotic events, as occurs with ESAs, which also increase erythropoietin levels. No trial has identified a hemoglobin target level, dose of Daprotab, or dosing strategy that does not increase these risks. Use the lowest dose of Daprotab 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

In the ASCEND-D trial, hospitalization for heart failure was observed in 7.5% (3.3 per 100 Person Years [PY]) of patients on dialysis receiving Daprotab and 6.8% (3.0 per 100 PY) of patients receiving recombinant human erythropoietin (rHPO). Patients with a pre-existing history of heart failure were at increased risk of hospitalization for heart failure with Daprotab (14.5%; 6.8 per 100 PY) compared to rHPO (11.3%; 5.1 per 100 PY). Consider the patient's history of heart failure when deciding whether to prescribe Daprotab. Advise patients of the symptoms and signs of heart failure and to immediately report any worsening to their healthcare provider/pharmacist.

## Hypertension

Daprotab is contraindicated in patients with uncontrolled hypertension. In the ASCEND-D trial, worsening of hypertension occurred in 24% (12 per 100 PY) of patients receiving Daprotab and 24% (12 per 100 PY) of patients receiving rHPO. Serious worsening of hypertension occurred in 3.1% of patients receiving Daprotab, and 3.1% of patients receiving rHPO. Cases of hypertensive crisis including hypertensive encephalopathy and seizures have also been reported in patients receiving Daprotab. Periodically monitor blood pressure and adjust or initiate anti-hypertensive therapy as needed.

## Gastrointestinal Erosion

In the ASCEND-D trial, gastric or esophageal erosions occurred in 5.7% (2.5 per 100 PY) of patients receiving Daprotab and 6.6% (2.9 per 100 PY) of rHPO-treated patients. Serious erosions, including gastrointestinal bleeding and the need for red blood cell transfusions, were reported in 3.6% and 3.1% of those receiving Daprotab and rHPO, 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.

Advise 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 Daprotab 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. In a large cardiovascular outcomes trial in adults with anemia of CKD who were not on dialysis (ASCEND-ND), an increased risk of cardiovascular mortality, stroke, thromboembolism, serious acute kidney injury, hospitalization for heart failure, and serious gastrointestinal erosions was observed in patients treated with Daprotab compared to rHPO.

## Malignancy

Because increased hypoxia inducible factor (HIF)-1 levels may be associated with unfavorable effects on cancer growth, Daprotab has not been studied and is not recommended in patients with active malignancies. Malignancies were observed in 4.4% (1.9 per 100 PY) of patients treated with Daprotab and 5.2% (2.3 per 100 PY) of patients treated with rHPO. No evidence of increased carcinogenicity was observed in animal studies.

## ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

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

## DRUG INTERACTIONS

### CYP2C8 Inhibitors

Concomitant administration of strong CYP2C8 inhibitors (e.g., gemfibrozil) with Daprotab 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 Daprotab 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 Daprotab when initiating or stopping therapy with clopidogrel or a moderate CYP2C8 inhibitor during treatment with Daprotab.

### 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 Daprotab when initiating or stopping therapy with CYP2C8 inducers during treatment with Daprotab.

## OVERDOSAGE

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

## HOW SUPPLIED/STORAGE AND HANDLING

### How Supplied

Daprotab tablets contain 1 mg, 2 mg, 6 mg of daprodustat.

### Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F to 86°F).

### Pregnancy

Daprotab may cause fetal harm. Advise females to inform their healthcare provider of a known or suspected pregnancy.

### Lactation

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

## DOSE

Store below 30°C

Protect from sunlight, heat and moisture.

Keep away from the reach of the children



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**GENOME PHARMACEUTICALS (PVT.) LTD.**  
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ALLIANZE MED PHARMA

خوراک:

ڈاکٹری ہدایت کے مطابق استعمال کریں۔

ہدایات:

رہتی، نمی اور گرمی سے محفوظ رکھیں۔

تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

دوا کو 30°C سے کم درجہ حرارت پر رکھیں۔