DOSING GUIDE

ORAL *JESDUVROQ (daprodustat)*

The first and only FDA-approved oral HIF PH inhibitor for Anemia due to Chronic Kidney Disease (CKD) in adults who have been receiving dialysis for at least four months.

INDICATION

JESDUVROQ 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

JESDUVROQ has not been shown to improve quality of life, fatigue, or patient well-being.

JESDUVROQ 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.

IMPORTANT SAFETY INFORMATION

WARNING : INCREASED RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, and THROMBOSIS OF VASCULAR ACCESS

- **JESDUVROQ 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.**
- **No trial has identified a hemoglobin target level, dose of JESDUVROQ, or dosing strategy that does not increase these risks.**
- **Use the lowest dose of JESDUVROQ sufficient to reduce the need for red blood cell transfusions.**

Please see additional Important Safety Information throughout. Please see full Prescribing Information, including BOXED WARNING and Medication Guide, at JESDUVROQhcp.com.

HIF PH, hypoxia-inducible factor-prolyl hydroxylase.

Jesduvroq
(daprodustat) tablets
1 mg • 2 mg • 4 mg • 6 mg • 8 mg

An oral HIF PH inhibitor for Anemia due to CKD in adults who have been receiving dialysis for at least four months

Dosage and Administration

Pre-Treatment and On-Treatment Evaluations of Anemia, Iron Stores, and Liver Tests

Evaluation of Anemia and Iron Stores

Correct and exclude other causes of anemia (e.g., vitamin deficiency, metabolic or chronic inflammatory conditions, bleeding) before initiating JESDUVROQ. Evaluate the iron status in all patients before and during treatment with JESDUVROQ. Administer supplemental iron therapy when serum ferritin is less than 100 ng/mL or when serum transferrin saturation is less than 20%. The majority of patients with CKD will require supplemental iron during the course of therapy.

Liver Testing

Assess serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and total bilirubin prior to initiation of JESDUVROQ. Repeat the liver tests if the patient develops signs or symptoms that could be consistent with liver disease during treatment with JESDUVROQ.

Important Dosing Information

Individualize dosing and use the lowest dose of JESDUVROQ sufficient to reduce the need for red blood cell transfusions. Do not target a hemoglobin higher than 11 g/dL.

JESDUVROQ can be taken with or without food, and without regard to concomitant administration of iron or phosphate binders.

JESDUVROQ should be swallowed whole. Tablets should not be cut, crushed, or chewed.

JESDUVROQ can be administered without regard to the timing or type of dialysis.

If a dose of JESDUVROQ 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.

IMPORTANT SAFETY INFORMATION (cont.)

CONTRAINDICATIONS

JESDUVROQ is contraindicated in patients:

- Receiving a strong CYP2C8 inhibitor such as gemfibrozil.
- With uncontrolled hypertension.

WARNINGS AND PRECAUTIONS

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

JESDUVROQ 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 JESDUVROQ.

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 JESDUVROQ, or dosing strategy that does not increase these risks. Use the lowest dose of JESDUVROQ 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.

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CKD, chronic kidney disease; HIF PH, hypoxia-inducible factor-prolyl hydroxylase.

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Recommended Starting Dose of JESDUVROQ

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

Adults Not Being Treated with an ESA: For adults not being treated with an ESA, the starting dose of JESDUVROQ is based on the hemoglobin level (see Table 1). Dose modifications are needed for patients receiving concomitant treatment with a moderate CYP2C8 inhibitor or moderate hepatic impairment.

Table 1. Starting Dose of JESDUVROQ for Adults on Dialysis not Receiving an Erythropoiesis-Stimulating Agent

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

*See dosing modifications (page 5) if the patient has moderate hepatic impairment and if the patient is on a moderate CYP2C8 inhibitor.

Adults Being Switched from an ESA: For adults being switched from an ESA to JESDUVROQ, the starting dose of JESDUVROQ is based on the dose regimen of the ESA at the time of substitution (see Table 2). Dose modifications are needed for patients receiving concomitant treatment with a moderate CYP2C8 inhibitor or moderate hepatic impairment.

Table 2. Starting Dose of JESDUVROQ for Adults on Dialysis Switching from an Erythropoiesis-Stimulating Agent

Current Dose of ESA			Dose of JESDUVROQ*
Epoetin Alfa† 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	4 mg
Greater than 2,000 to less than 10,000	Greater than 30 to 150	Greater than 40 to 180	6 mg
Greater than or equal to 10,000 to less than 20,000	Greater than 150 to 300	Greater than 180 to 360	8 mg
Greater than or equal to 20,000	Greater than 300	Greater than 360	12 mg

ESA, erythropoiesis-stimulating agent.

*See dosing modifications (page 5) if the patient has moderate hepatic impairment and if the patient is on a moderate CYP2C8 inhibitor.

†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.

IMPORTANT SAFETY INFORMATION (cont.)

Risk of Hospitalization for Heart Failure

Hospitalization for heart failure was observed in 7.5% (3.3 per 100 Person Years [PY]) of patients on dialysis receiving JESDUVROQ and 6.8% (3.0 per 100 PY) of patients receiving recombinant human erythropoietin (rhEPO). Patients with a pre-existing history of heart failure were at increased risk of hospitalization for heart failure with JESDUVROQ (14.5%; 6.8 per 100 PY) compared to rhEPO (11.3%; 5.1 per 100 PY).

Consider the patient's history of heart failure when deciding whether to prescribe JESDUVROQ. Advise patients of the symptoms and signs of heart failure and to immediately report any worsening to their healthcare provider.

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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 JESDUVROQ, consider hemoglobin rate of rise, rate of decline and hemoglobin variability. Do not increase the dose of JESDUVROQ more frequently than once every 4 weeks.

- If the dose of JESDUVROQ needs to be adjusted, increase or decrease by one dose level at a time (see Table 3).
- Decrease the dose of JESDUVROQ if hemoglobin increases rapidly (e.g., greater than 1 g/dL over 2 weeks or greater than 2 g/dL over 4 weeks) or if the hemoglobin exceeds 11 g/dL.
- If hemoglobin exceeds 12 g/dL, interrupt treatment with JESDUVROQ. When the hemoglobin is within the target range, treatment may be restarted at one dose level lower (see Table 3).
- Treatment with JESDUVROQ 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 JESDUVROQ

Daily dose of JESDUVROQ	1 mg	2 mg	4 mg	6 mg	8 mg	12 mg	16 mg	24 mg*

*24 mg is the maximum recommended once daily dose.

IMPORTANT SAFETY INFORMATION (cont.)

Hypertension

JESDUVROQ is contraindicated in patients with uncontrolled hypertension. Worsening of hypertension occurred in 24% (12 per 100 PY) of patients receiving JESDUVROQ and 24% (12 per 100 PY) of patients receiving rhEPO. Serious worsening of hypertension occurred in 3.1% of patients receiving JESDUVROQ and 3.1% of patients receiving rhEPO. Cases of hypertensive crisis including hypertensive encephalopathy and seizures have also been reported in patients receiving JESDUVROQ. Monitor blood pressure and adjust or initiate anti-hypertensive therapy as needed.

Gastrointestinal Erosion

Gastric or esophageal erosions occurred in 5.7% (2.5 per 100 PY) of patients receiving JESDUVROQ and 6.6% (2.9 per 100 PY) of rhEPO-treated patients. Serious erosions, including gastrointestinal (GI) bleeding and the need for red blood cell transfusions, were reported in 3.6% and 3.1% of those receiving JESDUVROQ and rhEPO, respectively. Consider this risk particularly in patients at increased risk for GI erosions, such as those with a history of GI erosion, peptic ulcer disease, use of concomitant medications that increase the risk of GI 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.

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Dosage Modification for Hepatic Impairment

Reduce the starting dose of JESDUVROQ 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 1 mg.

Use of JESDUVROQ 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 JESDUVROQ by half (see Tables 1 and 2) in patients who are on clopidogrel or a moderate CYP2C8 inhibitor except in patients whose starting dose is already 1 mg.

Monitor hemoglobin and adjust the dose of JESDUVROQ when initiating or stopping therapy with clopidogrel or a moderate CYP2C8 inhibitor during treatment with JESDUVROQ.

Dosage Forms and Strengths

1 mg, gray, biconvex, round film-coated tablets debossed with “GS KF” on one face.

2 mg, yellow, biconvex, round film-coated tablets debossed with “GS V7” on one face.

4 mg, white, biconvex, round film-coated tablets debossed with “GS 13” on one face.

6 mg, pink, biconvex, round film-coated tablets debossed with “GS IM” on one face.

8 mg, orange, biconvex, round film-coated tablets debossed with “GS 5E” on one face.

Tablets shown not actual size and may not represent actual color.

IMPORTANT SAFETY INFORMATION (cont.)

Serious Adverse Events in Patients with Anemia Due to Chronic Kidney Disease and Not on Dialysis
The safety of JESDUVROQ 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 an increased risk of cardiovascular mortality, stroke, thromboembolism, serious acute kidney injury, hospitalization for heart failure, and serious GI erosions was observed in patients treated with JESDUVROQ compared to rhEPO.

Malignancy
Because increased hypoxia inducible factor (HIF)-1 levels may be associated with unfavorable effects on cancer growth, JESDUVROQ 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 JESDUVROQ and 5.2% (2.3 per 100 PY) of patients treated with rhEPO. No evidence of increased carcinogenicity was observed in animal studies.

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IMPORTANT SAFETY INFORMATION (cont.)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥10%) are hypertension, thrombotic vascular events, and abdominal pain.

DRUG INTERACTIONS

Moderate CYP2C8 Inhibitors: Concomitant administration of moderate CYP2C8 inhibitors (e.g., clopidogrel) increases daprodustat exposure. Reduce the starting dose of JESDUVROQ by half when initiating treatment in patients on a moderate CYP2C8 inhibitor except in patients whose starting dose is already 1 mg. Monitor hemoglobin and adjust the dose of JESDUVROQ when initiating or stopping therapy with a moderate CYP2C8 inhibitor during treatment with JESDUVROQ.

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 JESDUVROQ when initiating or stopping therapy with CYP2C8 inducers during treatment with JESDUVROQ.

USE IN SPECIFIC POPULATIONS

Pregnancy: JESDUVROQ may cause fetal harm. CKD is associated with maternal and fetal risks. Advise pregnant women of the potential risk to the fetus.

Lactation: Given the serious adverse reactions seen in adults treated with JESDUVROQ, such as thrombotic vascular events, advise patients not to breastfeed during treatment with JESDUVROQ, and for one week after the final dose.

Hepatic Impairment: Reduce the starting dose of JESDUVROQ by half in patients with moderate hepatic impairment (Child-Pugh Class B) except in patients whose starting dose is already 1 mg. JESDUVROQ has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and is not recommended in these patients.

DRUG ABUSE AND DEPENDENCE

Abuse: Abuse of JESDUVROQ may be seen in athletes for the effects on erythropoiesis. There are no data on the abuse of JESDUVROQ in humans. Misuse of drugs that increase erythropoiesis, such as JESDUVROQ, by healthy persons may lead to polycythemia, which may be associated with life-threatening cardiovascular complications.

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Reference: JESDUVROQ [package insert]. Research Triangle Park, NC. GlaxoSmithKline; 2023.

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