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New Drug Evaluation: Jesduvroq (daprodustat) oral tablets

Date of Review: December 2023
Generic Name: daprodustat

End Date of Literature Search: 09/13/23
Brand Name (Manufacturer): JESDUVROQ (GlaxoSmithKline)

Dossier Received: yes

Plain Language Summary:

- The United States (US) Food and Drug Administration (FDA) approved a new medicine called daprodustat for anemia in adults with chronic kidney disease (CKD) who have been on dialysis for at least 4 months. It should not be prescribed for people who are not on dialysis and should not be used as a substitute when someone needs a blood transfusion to urgently correct an anemia. It is taken by mouth.
- Chronic kidney disease happens when the kidneys do not filter the blood as well as they should, and the ability of the kidneys to filter blood is not likely to improve. When chronic kidney disease is severe a person may need dialysis. Dialysis is a treatment to clean the body's blood when the kidneys are not able to. It helps remove waste and extra fluid from the blood. Most people with chronic kidney disease have anemia.
- Anemia due to chronic kidney disease is a condition where the body does not have enough red blood cells to carry oxygen throughout the body. Red blood cells carry oxygen from the lungs to the rest of the body. Anemia can make people feel tired or out of breath and may increase the need for a blood transfusion. This type of anemia is very common in people on dialysis.
- Medicines called erythropoiesis stimulating agents have been used for this type of anemia for decades. These drugs must be injected, and they can increase the risk of blood clots, stroke, heart attack, and death.
- Evidence shows that daprodustat increased hemoglobin (Hb), a type of measurement of red blood cells, in patients with anemia and chronic kidney disease who are on dialysis. It did not improve anemia more than erythropoiesis stimulating agents.
- Daprodustat has a similar number of severe side effects as erythropoiesis stimulating agents in patients on dialysis. Evidence does not show that daprodustat is safer than erythropoiesis stimulating agents and has similar warnings for blood clots, stroke, heart attack, and death
- We recommend that daprodustat be non-preferred, and that providers explain why someone needs daprodustat before Medicaid will pay for it. This process is called prior authorization.

Research Questions:

1. What are the comparative benefits and harms of daprodustat in patients with chronic kidney disease (CKD)?
2. Are there subgroups of patients for which daprodustat is more effective or cause more harm than other available options (e.g. erythropoiesis stimulating agents [ESA])?

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Conclusions:

- The efficacy and safety of daprodustat was evaluated in 5 global clinical studies[1-5], 3 of which included dialysis patients. The phase 3, open-label, ESA-controlled ASCEND-D study was the primary trial used by the FDA to support approval.[1]
- When daprodustat was compared to ESAs (intravenous [IV] epoetin alfa or subcutaneous [SC] darbepoetin alfa), both therapies had similar improvements in hemoglobin (Hb) over 28 to 52 weeks in patients with anemia of CKD on dialysis based on moderate quality evidence (ASCEND-D: daprodustat 0.28±0.02 g/dL vs. ESA 0.10±0.02 g/dL; mean adjusted difference, 0.18; 95% confidence interval [CI] 0.12 to 0.24; P<0.001 for noninferiority).[1]
- There is moderate quality evidence of no difference in first major adverse cardiac event (MACE) after randomization between daprodustat and ESAs (ASCEND-D: daprodustat 25.2% vs. ESA 26.7%; hazard ratio [HR] 0.93; 95% CI 0.81 to 1.07, p<0.001 for noninferiority).[1]
- Daprodustat has a box warning similar to ESA medications regarding the increased risk for death, serious adverse cardiovascular reactions, and stroke in patients with CKD on dialysis when the medication is administered to a target Hb level greater than 11 g/d.[6]
- There is insufficient long-term evidence for the use of daprodustat. Most results are applicable to White patients, though Black patients were well represented in the US cohort of the ASCEND-D trial.[1] Patients not on dialysis have more risk of harm compared to ESAs, and should not use daprodustat.[7,8]

Recommendations:

- Maintain daprodustat as non-preferred on the preferred drug list (PDL).
- Implement proposed PA criteria to ensure appropriate and safe use.
- After evaluation of costs in executive session, no PDL changes are recommended.

Background:

Anemia of chronic disease is a common complication of chronic kidney disease (CKD). Prevalence of CKD is 15% of the US population, and 17 million people have stage 3 to 5 disease.[8] Anemia affects 90% of those on dialysis (stage 5).[8] Patients often require blood transfusions and suffer from anemia related symptoms such as fatigue. The current standard of care are ESAs (e.g., epoetin alfa, darbepoetin alfa, epoetin beta) which stimulate red blood cell (RBC) production in the bone marrow and are approved for both dialysis dependent (DD) and non-dialysis dependent (NDD) anemia. Most patients have a concomitant absolute or functional iron deficiency and receive concomitant iron replacement. All ESA products are injectable (IV or SC).[8] ESA use in CKD has been found to increase major adverse cardiovascular events (MACE) and this is exacerbated by higher Hb targets.[8] While there is no identified target value, the Kidney Disease Improving Global Outcomes Clinical Practice Guidelines (KDIGO) guidelines advise against maintaining Hb above 11.5 g/dL and does not recommend starting ESA treatment in NDD patients with Hb at or greater than 10 g/dL.[8] These agents have a boxed warning for cardiovascular events with increased risk of death, myocardial infarction (MI), stroke, venous thromboembolism.[7,8] Additionally, for patients with certain types of cancer, there are boxed warnings for risk of tumor progression and recurrence. If used before surgery, there are risks for deep vein thrombosis (DVT), and DVT prophylaxis is recommended.[7]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Daprodustat (JESDUVROQ) is a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF PHI).[6] Daprodustat was submitted to the FDA with the applicant-proposed indication of "treatment of anemia due to CKD in adult patients on dialysis and not on dialysis", but after review, the FDA approved daprodustat for "treatment of anemia due to CKD in adults who have been receiving dialysis for at least 4 months" with a maximum daily dose of 24 mg.[8] Daprodustat is the first oral dosage form in the US for treatment of anemia; current ESAs are only available as injectable drugs. Product labeling limitations state daprodustat has not been shown to improve quality of life, fatigue, or patient well-being, and that it is not indicated as a substitute for transfusion in patients requiring immediate correction of anemia or in patients who are not on dialysis.[6]

Five global phase III studies[1-5] (**Table 3**) with different patient populations (e.g. dialysis dependent [DD] and non-dialysis dependent [NDD]), comparators, and dosing intervals (e.g. thrice weekly) were assessed by the FDA for approval.[8] Daprodustat was studied in hemodialysis, peritoneal dialysis, and non-dialysis patients in additional non-global studies conducted in Japan.[9-12] Those enrolling a study population of more than 100 patients are summarized in **Table 4**.[9,10] It was determined that both DD and NDD populations showed efficacy with daprodustat in increased Hb similar to ESAs, however differing safety findings between the 2 groups led to the more restrictive labeling than requested by the manufacturer.[8] Daprodustat is the first marketed HIF PHI. Two HIF PHI products (roxadustat and vadadustat) have been issued complete response letters (i.e., denials of approval) due to thrombosis and thromboembolic risk above the ESA standard of care and safety issues including liver injury (vadadustat).[8] Daprodustat is approved in Japan and roxadustat is approved in both Japan and the European Union.[13]

The Anemia Studies in Chronic Kidney Disease: Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor Daprodustat-Dialysis (ASCEND-D) study was used as the primary basis for approval in the DD population (**Table 2**).[1,8] This randomized, open-label, phase III trial compared treatment with daprodustat versus an ESA.[1] Adult patients with CKD and on dialysis for at least 90 days and an ESA for at least 6 weeks, with a baseline Hb of 8.0 to 11.5 g/dL were screened into a 4-week placebo plus ESA run-in period.[1] People with compliance between 80% and 120% with placebo during the run-in were randomized to open-label treatment with daprodustat or continuation of ESA. Daprodustat dosing was based on previous ESA dose and adjusted using an algorithm based on Hb level.[1] A rescue algorithm for IV iron, red blood cell (RBC) transfusion, and iron management was also provided.[1]

Block style 1:1 randomization with stratification occurred in 2964 patients.[1] The groups were well balanced with a median age of 58-59 years and median body mass index (BMI) of 26.8 kg/m^2. Of enrolled participants, 57.3% were male, 67% were White, 15.6% were Black (39.0% Black in US cohort), 44.9% had preexisting CV disease, and 17.4% had a preexisting thromboembolic event.[1] Malignancy within the previous 2 years (or basal cell cancer within 4 weeks) was an exclusion criteria and 4.9% of patients had coexisting cancer.[1] New or recurrent cancer (except localized squamous cell or basal cell carcinoma of the skin) was a prespecified reason to discontinue randomized treatment.[1] Eight percent of each group withdrew from the study, while 53% prematurely discontinued the study drug in each group but were followed to study completion or death.[8] Drug discontinuation reasons were similar between groups and included adverse event (16%), protocol-defined cessation criteria (e.g. cancer, pregnancy, rescue therapy, liver abnormalities, prohibited medication use) (15-16%), kidney transplant (9%), and death while on treatment (8%).[8]

The primary efficacy endpoint of mean change in Hb level from baseline to weeks 28 through 52 met noninferiority criteria (noninferiority margin -0.75 g/dL) with change in daprodustat 0.28$\pm$0.02 g/dL and ESA 0.10$\pm$0.02 g/dL (mean adjusted difference, 0.18; 95% CI 0.12 to 0.24; P<0.001).[1] Missing values were imputed using multiple imputation on the assumption that data were missing at random.[1]

This open-label trial introduced potential performance bias, though endpoints were objective or adjudicated by a blinded independent assessment committee. While few patients withdrew from the study, more than half discontinued the study medications for various reasons. Attrition was similar between groups but magnitude of drug effects may be reduced. This medication was appropriately studied versus the current standard of care.

Clinical Safety:
The primary noninferiority safety outcome was first occurrence of an adjudicated MACE after randomization as a composite of death from any cause, nonfatal MI, or nonfatal stroke.[1] The noninferiority margin was changed from 1.20 to 1.25 to speed trial closeout during the coronavirus disease 2019 pandemic.[1] Daprodustat was found non-inferior to ESA for first MACE (25.2% vs 26.7%; HR 0.93; 95% CI 0.81 to 1.07, p<0.001).[1] Adverse events occurring in more than 5% of daprodustat patients compared to ESAs were hypertension (24% for both), abdominal pain (11% vs. 8%), dizziness (7% vs. 6%), and hypersensitivity (7% for both).[6] Worsening of hypertension occurred in 19.8% of patient taking daprodustat and 20.5% of patients taking ESAs.[1]

The FDA assessment of safety findings between the DD and NDD patients led to the more restrictive labeling than requested by the manufacturer. Adjudicated cardiovascular (CV) endpoints in NDD patients showed elevated risks for stroke, thromboembolic disease, vascular access thrombosis, and MI relative to ESAs, and these risks were further increased in the US population.[8] There was also a possible increased risk of acute kidney injury in the NDD population and the oral route could lead to reduced healthcare encounters (with decreased monitoring) which may potentiate these effects if Hb increase is excessive or rapid.[8]

Daprodustat has a boxed warning for increased risk of death, MI, stroke, venous thromboembolism, and thrombosis of vascular access. This increased risk of thrombotic vascular events, including MACE, is further increased by targeting Hb greater than 11 g/dL.[6] No trial has identified an optimal Hb target level and the lowest dose sufficient to reduce the need for RBC infusions should be used.[6]

Contraindications include use with strong cytochrome P450 2C8 inhibitors (e.g. gemfibrozil) and uncontrolled hypertension, as well as warnings for risk of heart failure hospitalization in those with history of heart failure, hypertension, gastrointestinal erosion, malignancy, and use in NDD CKD patients where it is not indicated.[6]

The open-label study design may introduce bias when identifying and reporting of adverse events. The short duration and high drug discontinuation rate in both groups may make assessment of certain events, such as malignancy and MACE, incomplete.

Look-alike / Sound-alike Error Risk Potential: none

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Hematologic response as assessed by Hb levels
2) Need for transfusions due to anemia
3) Symptoms of anemia (e.g., fatigue)
4) Quality of life
5) Serious adverse events (e.g., mortality, MACE)
6) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Mean Hb change from baseline

Table 1. Pharmacology and Pharmacokinetic Properties.[6]

Parameter	
Mechanism of Action	Reversible inhibitor of HIF-PH1, PH2, and PH3, resulting in stabilization and nuclear accumulation of HIF-1α and HIF-2α transcription factors, leading to increased transcription of the HIF-responsive genes (including erythropoietin).
Oral Bioavailability	65%; not affected by high fat/high calorie meal compared to fasted state
Distribution and Protein Binding	Steady-state volume of distribution 14.2 L Plasma protein binding >99%
Elimination	18.9 L/h plasma clearance, 15 L/h blood clearance, hepatic extraction 18% 74% feces, 21% urine
Half-Life	1 - 4 hours
Metabolism	60% metabolites when radiolabeled daprodustat given to healthy adults

Abbreviations: HIF = hypoxia-inducible factor; h = hours; PHI = prolyl hydroxylase inhibitors; L = liters

Table 2. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Singh AK et al.[1,8,13] ASCEND-D NCT02879305 Phase 3, RCT, OL	1. Dapro oral starting between 4 and 12 mg daily 2. ESA: IV EPO if HD or SC DARB if PD Initial doses based on previous ESA dose. -4w placebo run-in period. Previous ESA therapy continued during screening and run-in period, People were randomized if were adherent to placebo and Hb 8.0-11.5 g/dL -Treatment-evaluated every 4w for 1y then every 12w until study	<u>Demographics</u>: Dapro; ESA -Median age 58y; 59y -White 66.9%; 66.5% -Black 15.3%; 15.8% -Asian 11.8%; 12.3% -HD 88.5%; 88.6% -Median BMI 26.8 -Time since dialysis started 0-2 y 30.5%; 30.5% 2 to <5y 36.0%; 35.8% >/= 5y 33.6%; 33.6% -ESA hyporesponsiveness 12.3%; 12.2% -CV disease 44.8%; 45.0% -Thromboembolic event 18.4%; 16.4% -Hb median 10.4 g/dL; 10.5 g/dL -median ferritin 589 ng/mL; 604 ng/dL	<u>ITT</u>: Dapro: 1487 ESA: 1477 <u>Attrition</u>: Withdrawn Dapro: 117 (8%) ESA: 111 (8%) <u>Drug discontinuation for reason other than death</u>: Dapro: 45.1% ESA: 44.8% <u>Died while taking study treatment:</u> Dapro: 8% ESA: 8%	<u>Primary Endpoints</u> (non-inferiority): Mean change (±SE) in Hb level from baseline to average during primary evaluation period (28-52w) Non-inferiority margin -0.75 g/dL 1. 0.25±0.02 g/dL 2. 0.10±0.02 g/dL Mean adjusted difference 0.08 95% CI 0.12 to 0.24 p-value<0.001 <u>Secondary Endpoint (Superiority assessment)</u>: -Average monthly dose of IV iron from baseline to week 52 1. 90.8±3.3 mg 2. 99.9±3.3 mg Mean difference -9.1 mg 95% CI -18.4 to 0.2	NA NA	<u>Outcome</u>: Primary Safety Endpoint (non-inferiority): First occurrence of adjudicated MACE, composite of death from any cause, nonfatal MI, Nonfatal stroke Non-inferiority margin 1.20 then amended to 1.25 to speed trial closeout due to coronavirus pandemic. 1. 374 (25.2%) 2. 394 (26.7%) HR 0.93 95% CI 0.81 to 1.07 p-value<0.001	NA	**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: (Low) 1:1 block randomization with stratification. Baseline characteristics appeared balanced. <u>Performance Bias</u>: (High) OL design (Investigators and patients knew assignment, sponsor and steering committee unaware of aggregate treatment assignments throughout the trial.) <u>Detection Bias</u>: (Low) OL design with objective primary efficacy outcome (Investigators and patients knew assignment, sponsor and steering committee unaware of aggregate treatment assignments throughout the trial.) MACE adjudication conducted by a blinded independent committee led by the Duke Clinical Research Institute. <u>Attrition Bias</u>: (High) High drug discontinuation but balanced between groups. Missing data handled appropriately with multiple imputation using "missing at random" assumption to handle missing Hb values. Tipping point analysis used as a sensitivity analysis to evaluate a "missing not at random" approach.

	target number of adjudicated first MACE events (945 events changed to 664 events with protocol update in July 2020) Median duration of follow up for CV events: 2.5 y (IQ 2.2-2.9 y) -1:1 block randomization stratified by type of dialysis, geographic region, and participation in ambulatory substudy monitoring blood pressure.	Key Inclusion Criteria: -Age 18-99y -CKD with dialysis for ≥ 90d -ESA ≥ 6w -Hb 8.0-11.5 g/dL -serum ferritin >100 mg/mL -Transferrin saturation >20% -Compliance with run-in placebo Key Exclusion Criteria: -Anemia unrelated to CKD -Recent CV event -Current or recent ca -Planned kidney transplant -Liver disease				AE leading to study withdrawal: 1. 1 (<1%), nonfatal 2. 0 (0%) Death: 1. 244 (16.4%) 2. 233 (15.8%)		Reporting Bias: (Low) Protocol and supplemental data available. Other Bias: (Unclear) Study sponsor and an academic steering committee designed and oversaw the trial conduct and analysis. Placebo run-in with adherence requirements before randomization. **Applicability**: Patient: Primarily studied in White participants but some racial diversity was included. Run-in period may screen for certain patient types. Intervention: Appropriate based on earlier trial phase dose testing. Comparator: Compared to ESA standard of care. Most commonly used ESA was epoetin alfa. Outcomes: Appropriate clinical markers for safety and efficacy. QoL changes not assessed. Setting: 431 centers in 35 countries

Abbreviations: ARR = absolute risk reduction; BMI = body mass index; ca = cancer; CI = confidence interval; CKD = chronic kidney disease; CV = cardiovascular; d= day; Dapro = daprodustat; DARB = darbepoetin alfa; dL = deciliter; EPO = epoetin alfa; ESA = erythropoiesis stimulating agent; g/= gram; Hb = hemoglobin; HD = hemodialysis; IQ = interquartile; ITT = intention to treat; IV = intravenous; MACE = major adverse cardiovascular event; mg = milligram; MI = myocardial infarction; mITT = modified intention to treat; N = number of subjects; NA = not applicable; ng = nanogram; NNH = number needed to harm; NNT = number needed to treat; OL = open-label; PD = peritoneal dialysis; PP = per protocol; QoL = quality of life; R = randomized controlled trial; SAE = serious adverse event; SC = subcutaneous; SE = standard error; tx = treatment; w = week; y = year.

Table 3: Summary of ASCEND Studies[8]

	Non-Dialysis Studies		Dialysis Studies		
	ASCEND-ND[5]	**ASCEND-NHQ[4]**	**ASCEND-D[1]**	**ASCEND-TD[2]**	**ASCEND-ID[3]**
Population	NDD Baseline ESA use or no baseline ESA use	NDD No recent ESA use	HD or PD Baseline ESA use	HD Baseline ESA use	ID No baseline ESA use
Daprodustat Dosing	Once Daily	Once Daily	Once Daily	Three Times a Week	Once Daily
Control	SC DARB	Oral placebo	IV EPO or SC DARB	IV EPO	SC or IV DARB
# of participants*	4500	600	3000	402	300
Blinding	OL (sponsor blind)	DB	OL (sponsor blind)	DB, DD	OL (sponsor blind)
Randomization	1:1	1:1	1:1	2:1	1:1

Stratification	• Region • Current ESA use • Participation in ABPM substudy	• Region	• Dialysis type (HD or PD) • Region • Participation in ABPM substudy	• Region	• Dialysis type (HD or PD) • Dialysis start planned or unplanned
Evaluation Period	Weeks 28-52	Weeks 24-28	Weeks 28-52	Weeks 28-52	Weeks 28-52
Hb target range	10-11 g/dL	11-12 g/dL	10-11 g/dL	10-11 g/dL	10-11 g/dL
Primary Outcome (efficacy)	Change in Hb from baseline NI margin -0.75 g/dL	Change in Hb from baseline Superiority 1-sided α 0.025	Change in Hb from baseline NI margin -0.75 g/dL	Change in Hb from baseline NI margin -0.75 g/dL	Change in Hb from baseline NI margin -0.75 g/dL
Primary Outcome Result	Mean ± SE Dapro: 0.66 ± 0.02 g/dL DARB: 0.74 ± 0.02 g/dL 0.08 g/dL difference 95% CI 0.03 to 0.13	Dapro: 1.58 g/dL PB: 0.19 g/dL AMD 1.40 g/dL 95% CI 1.23 to 1.56	Mean ± SE Dapro: 0.25 ± 0.02 g/dL ESA: 0.10 ± 0.02 g/dL AMD 0.08 95% CI 0.12 to 0.24	Adjusted mean ± SE Dapro: -0.04 ± 0.045 g/dL EPO: 0.02 ± 0.066 g/dL model-adjusted treatment difference -0.05 g/dL 95% CI -0.21 to 0.10	Adjusted mean ± SE Dapro: 1.02 ± 0.09 g/dL DARB: 1.12 ± 0.09 g/dL AMD -0.10 g/dL 95% CI -0.34 to 0.14
Primary Outcome (safety)	First MACE NI margin 1.25	NA	First MACE NI margin 1.25	NA	NA
First MACE	Dapro: 378/1937 (19.5%) DARB: 371/1935 (19.2%) HR 1.03 95% CI 0.89 to 1.19 NI margin 1.25	NA	Dapro: 374/1487 (25.2%) ESA: 394/1477 (26.7%) HR 0.93 95% CI 0.81 to 1.07 NI margin 1.25	NA	NA

Abbreviations: ABPM = ambulatory blood pressure monitoring; AMD = adjusted mean treatment difference; CI = confidence interval; Dapro = daprodustat; DARB = darbepoetin alfa; DB = double-blind; DD = double-dummy; dL = deciliter; EPO = epoetin alfa; ESA = erythropoiesis stimulating agent; g = grams; Hb = hemoglobin; HD = hemodialysis; HR = hazard ratio; ID = incident dialysis; IV = intravenous; MACE = major adverse cardiovascular event; NA = not applicable; NDD = non-dialysis dependent; NI = noninferiority; OL = open-label; PB = placebo; PD = peritoneal dialysis; SC = subcutaneous; SE = standard error.
*rounded

Table 4. Summary of Non-Global, Japan based Studies[9,10]

	Nangaku et al[9]	**Akizawa et al[10]**
Population	NDD Baseline or no baseline ESA use	HD Baseline ESA use
Daprodustat Dosing	Once Daily	Once Daily
Control	Epoetin beta pegol (route not stated)	IV DARB
# of participants*	299	271

	(Baseline ESA naïve participants [n=82] enrolled before protocol amendment to lower daprodustat starting dose in ESA naïve patients were excluded from ITT primary efficacy analysis.)	
Blinding	OL	DB, DD
Randomization	1:1	1:1
Stratification	• Current ESA use • Hb level	NA
Evaluation Period	Weeks 40-52	Weeks 40-52
Hb target range	11-13 g/dL	10-12 g/dL
Primary Outcome	Mean Hb NI margin -1.0 g/dL	Mean Hb NI margin -1.0 g/dL
Primary Outcome Result	Dapro: 12.0 g/dL 95% CI 11.8 to 12.1 Epoetin beta: 11.9 g/dL 95% CI 11.7 to 12.0 Difference 0.1 g/dL 95% CI -0.1 to 0.3	Dapro: 10.9 g/dL 95% CI 10.8 to 11.0 DARB: 10.8 g/dL 95% CI 10.8 to 11.0 Difference 0.1 g/dL 95% CI -0.1 to 0.2

Abbreviations: CI = confidence interval; Dapro = daprodustat; DARB = darbepoetin alfa; DB = double-blind; DD = double-dummy; dL = deciliter; ESA = erythropoiesis stimulating agent; g = grams; Hb = hemoglobin; HD = hemodialysis; ITT = intention to treat; IV = intravenous; NA = not applicable; NDD = non-dialysis dependent; NI = noninferiority; OL = open-label.

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use JESDUVROQ safely and effectively. See full prescribing information for JESDUVROQ.

JESDUVROQ (daprodustat) tablets, for oral use
Initial U.S. Approval: 2023

WARNING: INCREASED RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, and THROMBOSIS OF VASCULAR ACCESS.
See full prescribing information for complete boxed warning.

- **JESDUVROQ increases the risk of thrombotic vascular events, including major adverse cardiovascular events (MACE). (5.1)**
- **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. (5.1)**
- **No trial has identified a hemoglobin target level, dose of JESDUVROQ, or dosing strategy that does not increase these risks. (2.4)**
- **Use the lowest dose of JESDUVROQ sufficient to reduce the need for red blood cell transfusions. (2.4)**

----------INDICATIONS AND USAGE----------
JESDUVROQ is a hypoxia-inducible factor prolyl hydroxylase (HIF PH) inhibitor indicated for the treatment of anemia due to chronic kidney disease in adults who have been receiving dialysis for at least four months. (1)
Limitations of Use
Not shown to improve quality of life, fatigue, or patient well-being.
Not indicated for use:

- As a substitute for transfusion in patients requiring immediate correction of anemia.
- In patients not on dialysis.

----------DOSAGE AND ADMINISTRATION----------

- Administer orally once daily, with or without food. (2.2, 2.3)
- See Full Prescribing Information for starting dosage based on hemoglobin level, liver function and concomitant medications, and for dose titration and monitoring recommendations. (2.3, 2.4, 2.5, 2.6)

---------- DOSAGE FORMS AND STRENGTHS----------
Tablets: 1 mg, 2 mg, 4 mg, 6 mg, and 8 mg. (3)

---------- CONTRAINDICATIONS ----------

- Strong cytochrome P450 2C8 (CYP2C8) inhibitors such as gemfibrozil. (4)
- Uncontrolled hypertension. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Risk of Hospitalization for Heart Failure: Increased in patients with a history of heart failure. (5.2)
- Hypertension: Worsening hypertension, including hypertensive crisis may occur. Monitor blood pressure. Adjust anti-hypertensive therapy as needed. (5.3)
- Gastrointestinal Erosion: Gastric or esophageal erosions and gastrointestinal bleeding have been reported. (5.4)
- Not indicated for treatment of anemia of CKD in patients who are not dialysis-dependent (5.5)
- Malignancy: May have unfavorable effects on cancer growth. Not recommended if active malignancy. (5.6)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (incidence ≥10%) are hypertension, thrombotic vascular events, and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS----------

- Moderate CYP2C8 Inhibitors: Reduce starting dose. (7.1)
- CYP2C8 Inducers: Monitor hemoglobin and adjust the dose of JESDUVROQ as appropriate. (7.2)

---------- USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Breastfeeding not recommended until one week after the final dose. (8.2)
- Hepatic Impairment: Reduce the starting dose in patients with moderate hepatic impairment (Child-Pugh Class B). JESDUVROQ not recommended in severe hepatic impairment (Child-Pugh Class C). (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 2/2023

Daprodustat (JESDUVROQ)

Goal(s):
- To limit utilization to FDA-approved indications and in populations with proven safety

Length of Authorization:
- Up to 12 months

Requires PA:
- Pharmacy and physician administered claims

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this for anemia of chronic disease due to chronic kidney disease in an adult (18 years or older)?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Has the patient been on dialysis for at least 4 months?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Does the patient have a documented contraindication or intolerance to an erythropoiesis stimulating agent (ESA) (e.g., epoetin or darbepoetin)?	**Yes:** Go to #6	**No:** Go to #5
5. Does the patient have documented a lack of response to an ESA after at least 4 months of therapy?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
6. Is there documentation of active malignancy?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #7
7. Is there documentation that the patient has uncontrolled hypertension (≥140mmHg/≥90mmHg)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #8
8. Is the patient taking a strong cytochrome P450 2C8 inhibitor (example: gemfibrozil)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for 12 months (max 24 mg daily)

P&T/DUR Review: 12/23 (SF)
Implementation: 1/1/24