CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	216951
PDUFA Goal Date	February 01, 2023
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Reviewer Name(s)	Carla Darling, PharmD, BCPS
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	January 26, 2023
Subject	Evaluation of Need for a REMS
Established Name	Daprodustat
Trade Name	Jesduvroq
Name of Applicant	GlaxoSmithKline LLC
Therapeutic Class	Hypoxia-inducible factor prolyl-hydroxylase inhibitor
Formulation(s)	Oral Tablet
Dosing Regimen	1 mg, 2 mg, 4 mg, 6 mg, and 8 mg tablets, at a dosage of 1 mg to 24 mg once daily

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Jesduvroq (daprodustat) is necessary to ensure the benefits outweigh its risks. GlaxoSmithKline LLC (Applicant) submitted a New Drug Application (NDA 216951 for daprodustat with the proposed indication for the treatment of anemia due to chronic kidney disease (CKD) in adult patients who are dialysis-dependent (DD) and those who are not dialysis-dependent (NDD). The risks associated with daprodustat include major adverse cardiac events (MACE), hospitalization for heart failure (HHF), and bleeding gastric erosions. In the NDD population, there is also a possible increased risk of acute kidney injury (AKI). The applicant did not submit a proposed REMS or risk management plan with this application.

Anemia is common in patients with CKD and increases in severity as kidney disease progresses.[1] Erythropoiesis-stimulating agents (ESAs) are injectable therapies approved for anemia of CKD that are used after the other reversible causes of the anemia are addressed and include Epogen/Procrit (epoetin alfa), Aranesp (darbepoetin alfa), Mircera (methoxy polyethylene glycol-epoetin beta), and Retacrit (epoetin alfa-epbx).[2] As an oral therapy, daprodustat would offer an alternative route of administration compared to the currently approved intravenous ESA products for treating anemia associated with CKD.

During the course of the review, the Division of Non-malignant Hematology (DNH) identified safety issues with daprodustat treatment in the NDD population that are beyond that seen with ESAs including cardiovascular risks and risk of AKI. DNH determined that the benefit does not outweigh the risks of daprodustat in the NDD population; therefore, recommends against the approval of daprodustat for the treatment of anemia associated with CKD in the NDD population.

In the DD population, DRM and DNH have determined that a REMS is not needed to ensure the benefits of daprodustat outweigh its risks for the treatment of anemia due to chronic kidney disease (CKD) in adult patients who are dialysis dependent (DD). The efficacy of daprodustat was evaluated in two phase 3 trials, which the clinical reviewer determined provide substantial evidence of effectiveness based on the increase in Hb to a similar extent as approved ESAs.[3]

Based on the safety and efficacy information available, a REMS is not necessary to ensure the benefits outweigh the risks of daprodustat in the DD population. The risks associated with daprodustat in the DD population include MACE, hospitalization for heart failure, and gastrointestinal erosions/bleeding. Similar to approved ESAs, labeling will include the risk of MACE as a Boxed Warning; therefore, prescribers are likely aware of the risks and appropriate monitoring and management. If approved, labeling would include Warnings and Precautions to communicate the risks of MACE, hospitalization for heart failure, and gastrointestinal erosions/bleeding associated with daprodustat. These risks will also be communicated to patients and caregivers in a Medication Guide. At the time of this review, final labeling, and post-marketing requirements (PMRs) were still under negotiation. However, we anticipate post-marketing requirements to further evaluate the risks of MACE, hospitalization for heart failure, and gastrointestinal erosions/bleeding. If the applicant resubmits daprodustat for use in the NDD

population, a re-evaluation of the need for a REMS will be conducted at that time. If new safety information becomes available, DRM can re-evaluate the need for a REMS.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Jesduvroq (daprodustat) is necessary to ensure the benefits outweigh its risks. GlaxoSmithKline LLC (Applicant) submitted a New Drug Application (NDA) 216951 for daprodustat with the proposed indication for the treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis and not on dialysis. This application is under review in the Division of Non-malignant Hematology (DNH). The applicant did not submit a proposed REMS but proposed a Boxed Warning, Warnings and Precautions and a Medication Guide as part of labeling.

2. Background

2.1. Product Information

Daprodustat, a new molecular entity[a], is a reversible inhibitor of hypoxia-inducible factor (HIF) prolyl 4-hydroxylase (PH)1, PH2 and PH3. Inhibition of prolyl-4-hydroxylaze enzymes results in stabilization and accumulation of HIF-alpha.[4] Daprodustat stabilizes the HIF-alpha subunit that leads to increased transcription of the HIF-responsive genes.[5] Consequently, HIF prolyl hydroxylase inhibitors stimulate endogenous EPO production as well as improve iron metabolism.[4,6]

Daprodustat is proposed as 1 mg, 2 mg, 4 mg, 6 mg, and 8 mg tablets, at doses of 1 mg to 24 mg once daily administered orally and adjusted to maintain target hemoglobin levels of 10-11 g/dL.[b] The starting dose of daprodustat is based on the patient's hemoglobin (Hb) level, and current use of erythropoiesis-stimulating agent (ESA).

Daprodustat may be administered by patients or caregivers in the outpatient setting. If approved, daprodustat will be the first drug in the pharmacological class of hypoxia-inducible factor prolyl hydroxylase inhibitors. Daprodustat is currently approved in Japan for the treatment of anemia due to CKD.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 216951 relevant to this review:

- 02/01/2022: NDA 216951 submission for the treatment of anemia due to CKD in adult patients both on dialysis and not on dialysis received

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

- 10/26/2022: Cardiovascular and Renal Drugs Advisory Committee (AC) Meeting was convened to discuss whether the benefits of daprodustat outweigh its risks for the treatment of anemia due to CKD in adults who are not dialysis dependent (NDD) and those who are dialysis dependent (DD). The AC voted 11/5 against approval of daprodustat in adults who are not dialysis-dependent and 13/3 in favor of approval of daprodustat in adults who are dialysis dependent. A REMS proposal was not discussed.
- 11/21/2022: A Late Cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that no risk management actions have been identified to date; however, substantive review issues identified involve safety.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Chronic kidney disease (CKD) is a progressive, debilitating disease caused by damage to the kidneys from conditions such as diabetes, hypertension, glomerulonephritis, and polycystic kidney disease.[7] CKD is categorized into several stages (Stages 1-5 by severity) largely defined by the estimated glomerular filtration rate (eGFR) and need for dialysis. The 2012 Kidney Disease Improving Global Outcomes (KDIGO)[7] and the National Kidney Foundation (NKF) Kidney Disease Outcomes and Quality Initiative (KDOQI)[8] guidelines define CKD as kidney damage or a GFR <60 mL/min/1.73 m2 for more than 3 months. The guidelines define kidney damage as either functional abnormalities of the kidneys (such as proteinuria or albuminuria, or abnormalities of the urinary sediment, such as dysmorphic red cells) or structural abnormalities as noted on imaging studies.[9]

Kidney diseases are the 10th leading cause of death in the United States.[10] About 37 million US adults are estimated to have CKD and most are undiagnosed.[11] About 40% of people with severely reduced kidney function and not on dialysis are not aware of even having CKD.[11] Most patients are unaware of their declining kidney function until it is in its late stages or they succumb prematurely, typically to cardiovascular disease.[11] CKD prevalence in the adult U.S. population is estimated at about 14.4%; in certain groups, such as those aged ≥65 years where prevalence is about 36.8%.[12] When kidney damage is severe and kidney function is markedly compromised, patients will either die (largely of cardiovascular [CV] disease) or progress to end stage renal disease (ESRD) when either dialysis or a kidney transplant is needed for survival.[11] Morbidity and mortality are high among individuals with CKD. According to the United States Renal Data System (USRDS), in 2019 Medicare patients aged greater than 66 years with CKD had a mortality rate of 114.4 per 1,000 person years compared to 37.5 for patients without CKD.

Anemia is common in patients with CKD and increases in severity as kidney disease progresses.[1, c] Anemia is twice as prevalent in people with CKD (15.4%) as in the general population (7.6%), with an

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

estimated 4.8 million people affected in the US.[13,d] The anemia of CKD is multifactorial in etiology but is driven by both decreased erythropoietin (EPO) production by the failing kidney and altered iron homeostasis.[14,15]

3.2. Description of Current Treatment Options

The current standard of care for anemia of CKD includes oral or intravenous (IV) iron, ESAs, and red blood cell (RBC) transfusions to raise Hb levels that can lead to improved outcomes.[2,16] Guidelines also recommend checking for other reversible causes of anemia including vitamin B12 and folate and treating as needed.[2]

Patients with anemia of CKD are first iron repleted if needed, which can improve physical, cognitive, and immune function.[17] Iron is available in IV and oral formulations with different characteristics. IV formulations include the risk of iron overload and oral formulations are associated with poor absorption and adverse gastrointestinal side effects.[2,14]

ESAs are injectable therapies approved for anemia of CKD that can be used after the other reversible causes of the anemia are addressed and include Epogen/Procrit (epoetin alfa), Aranesp (darbepoetin alfa), Mircera (methoxy polyethylene glycol-epoetin beta), and Retacrit (epoetin alfa-epbx).[2] There is a box warning for all ESAs stating their risks (increased risk of death, cardiovascular events, thromboembolic events, stroke, and cancer) and recommending their use with the lowest dose as possible to avoid transfusions.[18]

If ESAs cannot be used or urgent correction of anemia is needed, RBC transfusions are considered but are associated with many risks including transmission of infection, iron overload, allergic reactions, and alloimmunization which can have implications for future kidney transplantation, the definitive therapy for CKD.[2,14]

4. Benefit Assessment

The efficacy and safety of daprodustat for the treatment of anemia in adult patients with CKD were evaluated in two Phase 3 clinical trials. The ASCEND-ND (NCT02876835) trial included the non-dialysis dependent (NDD) CKD population, and the ASCEND-D (NCT02879305) trial included the dialysis dependent (DD) CKD population. Three additional smaller trials, ASCEND-NHQ (NCT03409107), ASCEND-TD (NCT03400033) and ASCEND-ID (NCT03029208) were considered supportive.

The primary efficacy endpoint for the ASCEND-ND and the ASCEND-D trials was mean change in Hb between baseline and weeks 28 and 52. These trials were designed to show that treatment with daprodustat could achieve and maintain Hb within a prespecified target therapeutic range at least as effectively as active comparator (darbepoetin alfa or epoetin alfa). Non-inferiority was defined as being

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

achieved if the lower boundary of the 95% confidence interval (CI) of the treatment difference was greater than the non-inferiority margin of -0.75 g/dL.

Results in four of the five trials (ASCEND-ND, ASCEND-D, ASCEND-TD, and ASCEND-ID) showed non-inferiority of daprodustat to active comparator in the primary efficacy endpoints as measured by the mean change in Hb between baseline and weeks 28 and 52. For each trial the lower boundary of the 95% CI for the treatment difference was greater than the prospectively defined non-inferiority margin of -0.75 g/dL, thus demonstrating non-inferiority of daprodustat to active comparator (epoetin alfa or darbepoetin) in mean change in Hb from baseline. The 5th trial, ASCEND-NHQ, showed superiority of daprodustat to placebo in increasing and maintaining Hb levels to week 28.

The clinical reviewer concluded that the Applicant provided substantial evidence of effectiveness based on the increase in Hb to a similar extent as approved ESAs. [3, e]

5. Risk Assessment & Safe-Use Conditions

The safety database was comprised of participants from the ASCEND-D and ASCEND-ND trials. These two cardiovascular outcomes trials (CVOT) were designed to demonstrate non-inferiority of daprodustat to the active control with respect to the co-primary safety endpoint of time to first occurrence of adjudicated major adverse cardiac events (MACE), defined as a composite of all-cause mortality, non-fatal myocardial infarction (MI), and non-fatal stroke. Adjudicated secondary safety endpoints in both trials include all-cause mortality, cardiovascular (CV) mortality, fatal or nonfatal MI, stroke, hospitalization for heart failure (HHF), and fatal or nonfatal thromboembolic events (TEE).

The safety population for the NDD population is composed of 3,872 patients, with 1,937 patients who received daprodustat. The safety population for the DD population is composed of 2,964 patients with 1,487 patients who received daprodustat.[3] The most common adverse reactions reported in ≥5% in either population were hypertension, thrombotic vascular events, peripheral edema, constipation, abdominal pain, and hypersensitivity.[5]

The co-primary safety endpoint of MACE is discussed in more depth below (see Section 5.1). Additional key serious adverse events[f] including hospitalization for heart failure, gastrointestinal erosions, and acute kidney injury (AKI) are also discussed in more depth below (see Sections 5.2 and 5.3).

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[f] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization, or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Worsening hypertension, thrombotic vascular events, seizures, sepsis, and malignancy were similar in daprodustat treated groups to ESAs and are known risks associated with ESAs.[19,20] Similar to the ESAs, these risks will be communicated in the labeling (e.g. Prescribing Information and Medication Guide).

5.1. Major Adverse Cardiovascular Events (MACE)

The co-primary safety endpoint in both ASCEND-ND and ASCEND-D was the time to first occurrence of adjudicated MACE (composite of all-cause mortality, nonfatal MI, and nonfatal stroke). In both trials, the analyses for the primary safety endpoint ruled out risk of MACE by the pre-specified upper limit of the two-sided 95% confidence interval (CI) hazard ratio of less than 1.25. [g] In the ASCEND-ND trial, the hazard ratio for adjudicated MACE with daprodustat was 1.03 (95% CI: 0.89, 1.19) compared to darbepoetin. In the ASCEND-D population, the hazard ratio for adjudicated MACE with daprodustat was 0.93 (95% CI: 0.81, 1.07) compared to epoetin alfa. MACE and secondary CV endpoints in the DD and NDD populations are further discussed in more depth below.

5.1.1. Non-Dialysis Dependent (NDD) Population

Internal analyses of MACE and secondary CV endpoints suggest that daprodustat has elevated risks of MACE compared to ESAs in the NDD population. In the ASCEND-ND trial, results for prespecified subgroup analysis of MACE showed higher risk of MACE in the United States of America (USA) region (HR 1.19; 95% CI 0.91, 1.54). Notably, in the DNH's analyses of secondary CV endpoints in the ASCEND-ND trial, daprodustat appears to have higher risk of CV MACE (HR 1.11,CI 0.91-1.34), CV mortality (HR 1.20; CI 0.91, 1.58), MI (HR 1.06; CI 0.80,1.40), stroke (HR 1.33; CI 0.85, 2.07), HHF (HR 1.22; CI 0.95, 1.56), and TEE (HR 1.27; CI 0.88, 1.84) compared to darbepoetin.[g] Conclusions were unchanged with additional sensitivity analyses of secondary CV endpoints and the risk was greater when considering USA populations. Except for stroke, non-USA subgroup analyses had HRs of about 1.0, and USA subgroup analyses had elevated HRs (ranging from 1.21 to 2.03).

The clinical reviewer concluded that while ESAs like darbepoetin alfa already carry some of these cardiovascular risks, a further increase in these risks beyond that seen with the ESAs is concerning.[3] Due to these concerns along with the results and recommendations from the Cardiovascular and Renal Drugs Advisory Committee (CRDAC) meeting, DNH has decided not to approve daprodustat for use in the NDD population.

5.1.2. Dialysis Dependent (DD) Population

Daprodustat did not appear to show an increased risk of MACE or other cardiovascular events compared to darbepoetin alfa or epoetin alfa in the DD population. Additionally, in the DD population, there were no imbalances in the results for prespecified subgroup analysis of MACE. Notably, the agency's analysis of secondary CV endpoints showed that daprodustat appears to have a higher risk of HHF compared to

[g] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

epoetin alfa. In the ASCEND-D trial, and elevated hazard ratio for HHF (HR 1.10; CI 0.84, 1.45) was observed in the daprodustat arm compared to epoetin alfa.[h] The clinical reviewer concluded that daprodustat demonstrated non-inferiority (NI) to the ESAs for MACE and had a nominally favorable treatment difference in other cardiovascular events compared to darbepoetin alfa or epoetin alfa in the DD population.[3]

Similar to the ESAs, labeling for daprodustat will include the risk for MACE and serious cardiovascular and thromboembolic events in a Boxed Warning.[5,19] This risk will also be communicated in a Medication Guide.

5.2. Hospitalization for Heart Failure (HHF)

As mentioned above, the risk of HHF was higher with daprodustat compared to ESA in both the NDD and DD populations. Additional exploratory subgroup analysis in both NDD and DD populations showed a higher risk of HHF in patients with a history of heart failure. The HR for HHF in the subgroup with history of heart failure was 1.51 (95% CI 1.01, 2.25) in ASCEND-ND and 1.44 (95% CI 0.97, 2.14) in ASCEND-D.[h] In contrast, the HR for the subgroup without a history of heart failure was 0.99 (95% CI 0.72, 1.36) in ASCEND-ND and 0.91 (95% CI 0.63, 1.32) in ASCEND-D.

The risk of HHF will be communicated in Section 5, Warnings and Precautions of the label and in the Medication Guide.[3]

5.3. Serious Adverse Events

5.3.1. Gastrointestinal Erosions

In the ASCEND-ND and ASCEND-D trials, there was a higher number of adverse events of special interest for serious gastric/esophageal erosions in the daprodustat treated group compared to ESA. Differences in serious gastric erosion events were observed in both ASCEND-ND and ASCEND-D trials, with HR (95% CI): 1.63 (1.17,2.27) and HR (95% CI): 1.16 (0.78, 1.73), respectively.[3, h] The treatment arms in ASCEND-D and ASCEND-ND were balanced with respect to anti-platelet, anti-coagulant use, and prophylactic drugs (e.g., antiacids).

The clinical reviewer recommends communicating the risk of gastric erosions/bleeding in Section 5, Warnings and Precautions of the label and in the Medication Guide including a statement to avoid concomitant use with antiplatelets, NSAIDs, or anticoagulants, or in patients with a history of peptic ulcer disease or moderate to severe GERD.[3]

[h] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

5.3.2. Acute Kidney Injury (AKI)

In the ASCEND-ND trial, a treatment emergent serious adverse event of AKI showed a potential increased risk of AKI for daprodustat treated non-dialysis dependent patients compared to darbepoetin that seems to appear after 1 year on study. The relative risk of AKI was 1.47 (95% CI 1.07, 2.00) and risk difference of 1.54% [0.30, 2.79]).[3, i] Per the clinical reviewer, injury appears reversible with or without clinical interventions such as drug discontinuation.[3] Additionally, there were no differences detected for all-cause mortality or chronic kidney disease progression, which are important sequelae of AKI.

6. Expected Postmarket Use

The expected prescribers are likely nephrologists and internists as well as general practitioners. Daprodustat will likely be used in both inpatient and outpatient settings. It is expected that since daprodustat is an oral agent that could be prescribed without the coordination of a dialysis center, the prescriber and patient pool may be larger than that for ESAs, particularly for the NDD population.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for daprodustat beyond routine pharmacovigilance and labeling including a boxed warning.

8. Discussion of Need for a REMS

Dialysis Dependent Population

The clinical reviewer recommends approval of daprodustat for the treatment of anemia due to CKD in adults on dialysis based on the efficacy and safety information currently available. Chronic kidney disease (CKD) is a progressive, debilitating disease caused by damage to the kidneys. Anemia is common in patients with CKD and is primarily treated with intravenous ESAs. As an oral therapy, daprodustat would offer an alternative route of administration compared to the intravenous ESA products.

In three pivotal phase 3 clinical trials conducted in the DD population, daprodustat demonstrated non-inferiority to active comparator for the primary efficacy endpoint of mean change from baseline in Hb over weeks 28 to 52. The Division of Nonmalignant Hematology determined that there is substantial evidence that daprodustat increased Hb to a similar extent as approved ESAs. The most important safety concerns identified with the use of daprodustat in DD population include MACE, risk of hospitalization for heart failure and risk of bleeding gastric erosions.

The risk of MACE with daprodustat treatment in the DD population appears similar the risk with ESA comparator. Prescribers are likely familiar with the risk of MACE as the risk of adverse events (including

[i] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

MACE) is well documented for approved ESAs such as darbepoetin alfa and epoetin alfa.[19,20] Additionally, the risk of MACE with daprodustat will be communicated in a Boxed Warning similar to ESAs.

For the risk of hospitalization for heart failure (HHF) in the DD population, the review team identified a sub-population of patients without history of heart failure where the benefits of daprodustat treatment may outweigh the risk. However, there is no evidence in the clinical development program to suggest that the risk may be detected early to prevent worsening. Furthermore, the risk of HHF in patients treated with daprodustat is difficult to avoid in the DD population, as it cannot be effectively screened for in patients with multiple risk factors at baseline. The risk of hospitalization for heart failure will be communicated in Section 5, Warnings and Precautions of the label and in the Medication Guide.

For the risk of gastrointestinal erosions/bleeding in the DD population, there was no evidence in the clinical development program to suggest that the risk may be detected early to prevent worsening or that there is an effective clinical strategy to prevent the risk such as use of prophylactic drugs. The review team has not identified a way to effectively screen for those that may be at risk for gastrointestinal erosions/bleeding. This risk will be communicated in Section 5, Warnings and Precautions of the label and in the Medication Guide.[3]

Overall, the clinical reviewer concludes the safety profile of daprodustat in the DD population is acceptable. Based on the data available and that the prescribing community should be familiar with the risk of MACE, this reviewer concluded that if daprodustat should be approved in the DD population, a REMS is not necessary to ensure the benefits outweigh the risks. If approved, the risks associated with daprodustat will be communicated in labeling. At the time of this review, final labeling, and post-marketing requirements (PMRs) were still under negotiation. However, we anticipate post-marketing requirements to further evaluate the risks of MACE, hospitalizations for heart failure, and gastrointestinal erosions/bleeding for daprodustat

Non-Dialysis Dependent Population

During the course of the review, DNH identified safety issues with daprodustat for the proposed indication for the treatment of anemia due to chronic kidney disease (CKD) in adult patients who are NDD. In the NDD population, daprodustat treatment appeared to have additional risks of AKI and other cardiovascular risks that are beyond what was reported with ESAs in clinical trials used to support this application.

A Cardiovascular and Renal Drugs Advisory Committee Advisory Committee (CRDAC) meeting was held on October 26, 2022 to discuss whether the benefits of daprodustat outweigh its risks for the treatment of anemia due to CKD in adults who are NDD and those who are DD. Eleven committee members voted "No" and five members voted "Yes" against the benefits of daprodustat outweighing the risks in adults who are not dialysis dependent. In contrast, three members voted "No" and thirteen members voted "Yes" in favor of the benefits of daprodustat outweighing the risks in adults who are dialysis dependent. A REMS proposal was not discussed. (b) (4)

Due to concerns with the increase in cardiovascular risks beyond that seen with ESAs along with the results and recommendations from the CRDAC, DNH determined that the benefit does not outweigh the risks of daprodustat in the NDD population; therefore, DNH recommends against the approval of daprodustat for the treatment of anemia associated with CKD in the non-dialysis population.

9. Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits of daprodustat in the DD population outweigh the risks. The safety concerns associated with daprodustat use are similar to ESAs including the risk of MACE and healthcare providers who treat anemia of CKD are familiar with and able to appropriately monitor these risks. At the time of this review, labeling and PMR negotiations were ongoing.

If an applicant resubmits daprodustat for use in the NDD population, a re-evaluation of the need for a REMS will be conducted at that time. Should DNH have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10. Appendices

10.1. References

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