CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215192Orig1s000

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	215192
PDUFA Goal Date	March 27, 2024
Nexus TTT #	2023-7072
Reviewer Name	Victoria Sammarco, PharmD, MBA
	Timothy Bernheimer, PharmD
Team Leader	Carolyn Tieu, PharmD, MPH
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	March 25, 2024
Subject	Evaluation of Need for a REMS
Established Name	vadadustat
Trade Name	Vafseo
Name of Applicant	Akebia Therapeutics, Inc.
Therapeutic Class	hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor
Formulation	oral tablets
Dosing Regimen	Recommended starting dose: 300 mg daily
	Dose range 150 mg – 600 mg
	Titrated up or down in increments of 150 mg

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1. Introduction

This review by the Division of Risk Management (DRM) is an addendum to our March 17, 2022 risk evaluation and mitigation (REMS) determination review[1] to evaluate whether a REMS for the new molecular entity (NME) Vafseo (vadadustat) is necessary to ensure the benefits outweigh its risks.

Akebia Therapeutics, Inc. (hereafter referred to as the Applicant) originally submitted a New Drug Application (NDA) 215192 on March 29, 2021 for vadadustat with the proposed indication of the treatment of anemia associated with chronic kidney disease (CKD) in adults that are dialysis-dependent (DD-CKD) and non-dialysis dependent (NDD-CKD). DRM concluded that based on the information available, a REMS would not ensure the benefits outweigh the risks for vadadustat.[1] A Complete Response letter was issued to the Applicant on March 29, 2022 due to efficacy and safety issues in both the NDD-CKD and DD-CKD populations.[2] The primacy efficacy issue was the higher use of rescue therapy for worsening anemia with vadadustat compared to darbepoetin alfa, particularly for erythropoietin stimulating agent (ESA) rescue in the NDD-CKD population and for ESA and red blood cell (RBC) transfusion rescue in the DD-CKD population. The safety issues included (1) non-inferiority was not established for vadadustat compared to darbepoetin alfa on the primary safety endpoint of adjudicated major adverse cardiac events (MACE) in the NDD-CKD population, (2) a concerning signal for adjudicated thromboembolic (TE) events with vadadustat compared to darbepoetin alfa, an ESA with an established increased risk of TE events in the DD-CKD population, (3) concerns for a clinically significant risk for drug-induced liver injury (DILI) with vadadustat use.[2] The Applicant was advised to conduct new clinical trial(s) that establish a favorable benefit/risk assessment of vadadustat in a specific patient population or with a different dosing regimen.

The Applicant filed a request for formal dispute resolution on October 24, 2022 arguing that vadadustat should have been approved for the DD-CKD population.[3] This formal dispute resolution appeal was denied on May 26, 2023 but included a path forward for vadadustat use in the DD-CKD population if the additional safety data and analyses were submitted that addressed renal transplant rejection rates as a measure of the adverse outcomes associated with more RBC transfusion rates than ESAs.

The Applicant resubmitted NDA 215192 on September 27, 2023 for the proposed indication of the treatment of anemia associated with DD-CKD. The Applicant submitted additional safety data including post-marketing data from other countries where the drug is currently approved, updated hepatic expert report, and additional analyses of transplant rejection rate, gastric erosions and hemorrhage, and heart failure. The Applicant did not submit a proposed REMS or risk management plan with this resubmission. This application is under review in the Division of Non-hematologic Malignancies (DNH).

2. Background

2.1. Product Information

Refer to our March 17, 2022 REMS review for the product information.[1] Since our review, the Applicant has revised the indication for vadadustat, the proposed indication is for the treatment of anemia due to chronic kidney disease in adults on dialysis.

Since the REMS Determination review in 2022, vadadustat has been approved in the European Union (2023),[4] Norway (2023),[4] Iceland (2023),[4] Liechtenstein (2023),[4] United Kingdom (2023),[5] Switzerland (2023)[6] Australia (2023),[7] and Taiwan (2023).[8]

2.2. Regulatory History

The following is a summary of the regulatory history for vadadustat (NDA 215192) relevant to this review cycle:

- 03/29/2022: Complete Response issued to Applicant.
- 07/13/2022: A Type A meeting was held between the Agency and the Applicant to discuss the contents of the Complete Response Letter.
- 10/24/2022: Applicant submitted request for formal dispute resolution concerning the 03/29/22 Complete Response.
- 05/26/2023: Formal Dispute Resolution Appeal Denial letter sent to the Applicant.
- 09/27/2023: NDA 215192 resubmission for the treatment of anemia associated with chronic kidney disease in adults on dialysis received, subject of this review.

3. Therapeutic Context and Treatment Options

3.1. Description of Current Treatment Options

Refer to our March 17, 2022 REMS review for information on the therapeutic context and treatment options.[1] Since the REMS Determination review in 2022, another hypoxia-inducible factor prolyl hydroxylase inhibitor was approved. Jesduvroq (daprodustat) was approved in February 2023 for the treatment of anemia due to chronic kidney disease in adults who have been receiving dialysis for at least four months. Daprodustat has a box warning that communicates the increased risk of death, myocardial infarction, stroke, venous thromboembolism, and thrombosis of vascular access. Daprodustat labeling also communicates the risk of hospitalization for heart failure, hypertension, gastrointestinal erosion, serious adverse events in patients with anemia due to CKD and not on dialysis, and malignancy in the *Warnings and Precautions* section.[9] Daprodustat is not subject to a REMS.

Erythropoiesis stimulating agents (ESAs) are injectable therapies approved for anemia of CKD that include Epogen/Procrit (epoetin alfa), Aranesp (darbepoetin alfa), Mircera (methoxy polyethylene glycol-epoetin beta) and Retacrit (epoetin alfa-epbx) and can be used after the other reversible causes

of the anemia are addressed. All ESAs contain a box warning of increased risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access and tumor progression or recurrence.[10,11,12,13] yesESAs were previously subject to a REMS to support informed discussions between patients with cancer and their healthcare providers but the REMS was eliminated in 2017 due to reassuring drug utilization trends and changes to the Centers for Medicare and Medicaid Services National Coverage Determination. None of the approved ESAs are currently subject to a REMS.[14]

4. Benefit Assessment

Refer to the DRM review dated March 17, 2021[1] and the Integrated review dated March 29, 2021[15] for the benefit assessment. Additionally, refer to the formal dispute resolution denial letter, which included a path forward for vadadustat use in the DD-CKD population if the additional safety data and analyses were submitted that addressed renal transplant rejection rates as a measure of the adverse outcomes associated with more RBC transfusion rates than ESAs.

To address the higher use of ESA rescue therapy and red blood cell transfusion in vadadustat than darbepoetin alfa, the Applicant conducted prespecified sensitivity analyses where pre-visit hemoglobin values within four weeks of administration of rescue therapy were set to "missing" instead of the recorded values and vadadustat remained non-inferior to darbepoetin alfa. Additionally, subsequent analyses showed that the rate of renal transplant in the DD-CKD pooled population, 2.5% of patients and 3.8% of patients in the vadadustat and darbepoetin groups, respectively, had transplant rejection. The clinical reviewer concludes that there were minimal differences in the rate of renal transplant rejection over similar exposure durations, providing reassurance RBC transfusion rescue therapy did not lead to an increased rate of renal allograft rejection in patients who undergo kidney transplantation.

5. Risk Assessment & Safe-Use Conditions

The Applicant submitted several safety analyses to address the safety deficiencies in the Complete Response Letter.[2]

To address the concern of an increased risk for adjudicated TE events in the DD-CKD population, the Applicant submitted rates of access abandonment and revascularization procedures. The clinical reviewer concluded that access abandonment and need for revascularization procedures were observed at similar rates in the vadadustat group and darbepoetin alfa group.

To address the risk of DILI, the Applicant submitted a safety update report and postmarketing data following the approval of vadadustat in Japan in 2020. The safety update report summarizes all the available safety data for vadadustat since the 120-Day Safety Update Report was submitted following the initial NDA. This report also includes two new clinical studies of vadadustat in patients with DD-CKD (Study CI-0036 and Study CI-0039). Study CI-0036 was a phase 3b, randomized, open-label, active controlled study of vadadustat versus darbepoetin alfa for maintenance treatment of anemia in patients requiring hemodialysis, after conversion from ESA therapy in the US and Europe. Study CI-039 was a phase 3b, randomized, open-label, active controlled study evaluating the efficacy and safety of dose

conversion from epoetin beta to three times weekly oral vadadustat for the maintenance treatment of anemia in patients requiring hemodialysis.

The adverse events of special interest of gastric erosions and heart failure leading to hospitalization were not analyzed in the previous review. For this review cycle, studies CI-0036 and CI-0039 were analyzed for gastric erosions and heart failure leading to hospitalization in the DD-CKD population as these AESIs have been identified in the other approved HIF-PH inhibitor. Gastric erosions were observed with vadadustat in the DD-CKD population and NDD-CKD population in studies CI-0036 and CI-0039 and the clinical reviewer concludes this risk may be a class effect. The long-term risk will be assessed in a Post Marketing Requirement (PMR).

For heart failure leading to hospitalization, the statistical reviewer concluded that using adjudicated data from the original submission, this risk was not increased in the vadadustat arm compared to the darbepoetin arm. The clinical reviewer concluded that heart failure occurred at lower rates in the vadadustat group compared to the darbepoetin alfa group, however, there is limited long-term safety data, therefore the risk of heart failure will be further assessed in a PMR.

See below for the findings for the specific risks.

5.1. Increased Risk of Death, Myocardial Infarction (MI), Stroke, and Venous Thromboembolism, and Thrombosis of Vascular Access

The increased risk of MACE with vadadustat was seen in the NDD-CKD population and an increased risk for adjudicated thromboembolic (TE) events, due to an increase in events of vascular access thrombosis (VAT) in the DD-CKD population. The Applicant has revised the proposed indication to treatment of anemia associated with DD-CKD and proposed a *Limitation of Use* in the labeling that Vafseo is not for use in patients with anemia due to CKD not on dialysis. The Applicant conducted additional analyses on the serious consequences of VAT such as access abandonment and need for revascularization. In the DD-CKD population the rates of access abandonment occurred at 3.8% in the vadadustat treatment group and 4.4% in the darbepoetin alfa treatment group at Week 52. In the pooled DD-CKD population, rates of revascularization procedures occurred at 11.4% in the vadadustat treatment group and 12.9% in the darbepoetin alfa treatment group. The clinical reviewer concludes that access abandonment and need for revascularization procedures were observed at similar rates in the vadadustat group and darbepoetin alfa group.

Both of these risks will be conveyed in the box warning and the warnings and precautions section of labeling. The labeling will advise healthcare providers that Vafseo increases the risk of arterial and venous thrombotic events, that may be fatal, including myocardial infarction, stroke, venous thromboembolism and vascular access thrombosis. Healthcare providers are instructed to avoid use in patients with a history of myocardial infarction, cerebrovascular event, or acute coronary syndrome within the 3 months prior to starting Vafseo. The label will advise healthcare providers that a rate of hemoglobin rise of greater than 11g/dL over 2 weeks may contribute to these risks and that targeting a

hemoglobin level of greater than 11g/dL is expected to further increases the risk of death and arterial and venous thrombotic events, as occurs with ESAs, which also increase erythropoietin levels. The box warning in labeling will advise health care providers that no trial has identified a hemoglobin target level, dose of Vafseo, or dosing strategy that does not increase these risks.

5.2. Hepatotoxicity

As described in the CR letter, there was a concerning drug-induced liver injury (DILI) event and an imbalance in the incidence of alanine aminotransferase (ALT) elevations meeting higher cut points.

Review of the pooled analyses of all trials also identified a hepatotoxicity safety signal. One probable Hy's Law case, at least seven cases of probable DILI in Temple's Corollary and a higher incidence of cases detected in the higher alanine aminotransferase (ALT) categories in the vadadustat arm, compared to the darbepoetin alfa arm, there is a clinically significant hepatocellular injury risk with the use of vadadustat in patients with CKD. Studies CI-0036 and CI-0039, along with the post-marketing experience from Japan, did not identify additional adjudicated serious DILI cases.

Labeling will advise healthcare providers that Vafseo can cause hepatotoxicity and advise healthcare providers to measure ALT, AST, and bilirubin prior to the initiation of Vafseo and monthly after initiation for the first 6 months and then to monitor as clinically indicated.

Labeling will instruct prescribers to discontinue Vafseo if there is persistent ALT or AST >3x ULN or if ALT or AST elevations > 3x ULN are accompanied by a bilirubin increase >2x ULN.

5.3. Gastrointestinal Erosions

The statistical reviewer states that in studies CI-0016 and CI-0017 narrowly defined gastrointestinal erosion events occurred more frequently in the vadadustat arm than the darbepoetin arm (3.8 per 100 PY versus 3.2 per 100 PY). The estimated IRD (95% CI) and HR (95% CI) were 0.72 per 100 PY (-0.23 per 100 PY, 1.67 per 100 PY) and 1.23 (0.94, 1.59), respectively. Gastric or esophageal erosions occurred in 6.4% (4.6 per 100 PY) of patients receiving vadadustat and 5.3% (4.6 per 100 PY) of darbepoetin alfa treated patients. Serious gastrointestinal erosions were reported in 3.4% (2.3 per 100 PY) and 3.3% (2.05 per 100 PY) of those receiving vadadustat and darbepoetin alfa, respectively.

Labeling will advise healthcare providers to 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.

6. Expected Postmarket Use

The expected prescribers of vadadustat are likely nephrologists as the patient population is only indicated for patients with DD-CKD. Unlike injectable agents like ESAs which are administered by health care providers at the time of dialysis, vadadustat is an oral product dosed daily and may be self-administered in an outpatient setting.

7. Risk Management Activities Proposed by the Applicant

7.1. Other proposed Risk Management Activities

The Agency sent the Applicant a preliminary evaluation of anticipated Post Marketing Requirements (PMRs) for the Application on March 12, 2024 with the following post market requirements (PMRs):

PMR 1: Conduct an observational study to characterize the long-term safety (up to 5 years follow up) of Vafseo in adults with dialysis dependent chronic kidney disease treated with the approved dosing regimen of Vafseo in the United States. Specific safety outcomes of interest include: thrombotic vascular events including vascular access thrombosis; hospitalization for heart failure; and serious gastrointestinal bleeds.

PMR 2: Conduct an observational study (up to 5 years follow up) to assess the risk for malignancy (hematological and non-hematological) in dialysis dependent chronic kidney disease adults with anemia treated with Vafseo versus an erythropoiesis-stimulating agent (ESA) comparator arm.

PMR 3: Conduct a worldwide descriptive study to collect prospective and retrospective data on women exposed to Vafseo during pregnancy to assess the risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant.

PREA PMR: Conduct a trial to evaluate the safety, tolerability and pharmacokinetics, of Vafseo for the treatment of anemia associated with chronic kidney disease in children and adolescents aged 3 months to under 17 years requiring dialysis.

Reviewer Comments: *We note that these other activities are outside of the scope of the REMS and defer to Division of Epidemiology for review and input.*

8. Discussion of Need for a REMS

The Clinical Reviewer recommends approval for vadadustat on the basis of the overall benefit-risk profile is favorable, and the Applicant has adequately addressed all deficiencies in the CRL for the indication of anemia of DD-CKD.

The risks include increased risk of death, myocardial Infarction, stroke, and venous thromboembolism, and thrombosis of vascular access, hepatotoxicity and gastric erosion. The was an increased risk of MACE with vadadustat seen in the NDD-CKD population in the previous submission. The Applicant has revised the proposed indication to the treatment of anemia associated with DD-CKD and proposed a *Limitation of Use* in the labeling that Vafseo is not for use in patients with anemia due to CKD not on dialysis. The risks of increased risk of death, myocardial infarction, stroke, and venous thromboembolism, and thrombosis of vascular access will be communicated in the boxed warning and warnings and precautions section of labeling. ESAs, such as darbepoetin, and daprodustat are approved for the treatment of anemia due to CKD in patients on dialysis. These products carry the same risks and

the risks are communicated in the boxed warning and warnings and precautions section of labeling. These products are not subject to a REMS.[9,14]

ESAs are a mainstay of therapy for anemia in the DD-CKD population and are commonly prescribed by nephrologists and administered to DD-CKD patients at the time of dialysis. As a result, likely prescribers of vadadustat (nephrologists) are expected to have the knowledge of and are familiar with managing this risk.

For the risk of hepatoxicity, including DILI, this risk will be communicated through labeling and will be described in the *Warnings and Precautions* section of labeling. The labeling will advise healthcare providers to monitor patients through regular liver test monitoring. Such monitoring is routine among DD-CKD patients and the likely prescribers will have the knowledge of and are familiar with managing this risk. This risk will also be further assessed with enhanced pharmacovigilance.

Additionally, the PMR requiring the Applicant to complete and observational study on long-term safety may provide additional information that could aid in a better understanding of the risks and if additional risk mitigation strategies are needed in the future.

The reasons cited in the March 17, 2022 review of why a REMS to mitigate thromboembolic risks in the DD-CKD population would be unlikely to affect the benefit-risk balance are still relevant, but based on the revised indication, limitation of use and considering the addition safety information, this reviewer concludes that a REMS is not necessary to ensure the benefits outweigh the risks for vadadustat.

9. Conclusion & Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits outweigh the risks. In general, healthcare providers (likely nephrologists) who treat anemia associated with chronic kidney disease in adults on dialysis are familiar with and knowledgeable in managing the risks.

At the time of this review, evaluation of safety information and labeling was ongoing. Should DNH have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10. References

[1] Sammarco V. Division of Risk Management. NME REMS Determination Review for vadadustat, NDA 215192. March 17, 2022. DARRTS Reference ID: 4954328.

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[4] Akebia. Akebia Receives European Commission Approval for Vafeseo (vadadustat) for the Treatment of Symptomatic Anaemia Associated with Chronic Kidney Disease in Adults on Chronic Maintenance Dialysis.

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[11] Aranesp (darbepoetin alfa) injection Prescribing Information. Amgen Inc. Thousand Oaks, CA 91320. Revised January 2019; accessed at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/103951s5378lbl.pdf

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[13] Retacrit (epoetin alfa-epbx) injection Prescribing Information. Pfizer. New York, NY 10001. Revised April 2023; accessed at https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125545Orig1s022lbl.pdf

[14] Redd N. Division of Risk Management. Release of REMS for Erythropoiesis stimulating agents (ESAs). BLA 103951 and BLA 103234. January 5, 2017. DARRTS Reference ID: 4037649.

[15] Integrated Review and Evaluation: NDA 215192 Vafseo (vadadustat), oral tablets. March 29, 2021. DARRTS ID: 4960499; accessed at https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80653285

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/s/

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Division of Risk Management (DRM)
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Application Type	NDA
Application Number	215192
PDUFA Goal Date	March 29, 2021
OSE RCM #	2021-643
Reviewer Name	Victoria Sammarco, PharmD, MBA
Team Leader	Carolyn Tieu, PharmD, MPH
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	March 17, 2022
Subject	Evaluation of Need for a REMS
Established Name	Vafseo
Trade Name	vadadustat
Name of Applicant	Akebia Therapeutics, Inc.
Therapeutic Class	hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor
Formulation	oral tablets
Dosing Regimen	Recommended starting dose: 300 mg QD Dose range 150 mg – 600 mg Titrated up or down in increments of 150 mg

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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) Vafseo (vadadustat) is necessary to ensure the benefits outweigh its risks. Akebia Therapeutics, Inc. submitted a New Drug Application (NDA) 215192 for vadadustat with the proposed indication of the treatment of anemia associated with chronic kidney disease (CKD) in adults that are dialysis-dependent (DD-CKD) and non-dialysis dependent (NDD-CKD). This application is under review in the Division of Non-hematologic Malignancies. The applicant amended their submission on December 15, 2021 and proposed a REMS that consists of a

(b) (4)

2. Background

2.1. Product Information

Vadadustat, a new molecular entity[a], is part of the pharmacological class of hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitors and is indicated for the treatment of anemia associated with chronic kidney disease in adults on dialysis and not on dialysis. The inhibition of hypoxia-inducible factor prolyl hydroxylase leads to increased cellular levels of hypoxia-inducible factor thereby stimulating endogenous erythropoietin (EPO) production. EPO increases iron mobilization, hemoglobin, and red blood cell production.

Vadadustat will be supplied as 150 mg, 300 mg and 450 mg tablets. The proposed dosing regimen is 300 mg orally each day to start, titrating every 4 weeks as needed in increments of 150mg to achieve or maintain hemoglobin levels of 10-11 g/dL.[b] Proposed dosing includes that hemoglobin (Hb) levels should be monitored when initiating or adjusting therapy every two weeks until stable, then at least monthly. Further, if the Hb rises rapidly (e.g., more than 1 g/dL in any 2-week period or more than 2 g/dL in 4 weeks), dosing should be interrupted or reduced. If the Hb level exceeds 11 g/dL, dosing should be stopped until Hb is less than or equal to 11 g/dL and resumed with a dose that is 150 mg less than the dose prior to interruption. Vadadustat was submitted with a boxed warning that states that this class of medications has been shown to increase the risk of death, myocardial infarction, stroke, venous thromboembolism, and thrombosis of vascular access.

Currently, vadadustat is approved in Japan where there have been no new safety signals reported since the approval on June 29, 2020.

[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.*

2.2. Regulatory History

The following is a summary of the regulatory history for vadadustat (NDA 215192) relevant to this review:

- 03/29/2021: NDA 215192 submission for the treatment of anemia associated with chronic kidney disease in adults on dialysis and not on dialysis received.
- 11/18/2021: A Late-cycle meeting was held between the Agency and the Applicant via teleconference. The Applicant indicated that they would propose a communication plan REMS.
- 12/15/2021: Applicant submitted a proposal for a communication plan REMS.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

The etiology of anemia of CKD is multifactorial and could be due to decreases in erythropoietin (EPO) production, absolute or functional iron deficiency, and chronic inflammation, among other etiologies.[1] Anemia is relatively common in patients with chronic kidney disease (CKD), especially as estimated glomerular filtration rates (eGFRs) fall below 60 mL/min/1.73 m^2. Data from the National Health and Nutrition Examination Survey (NHANES) showed that the prevalence of anemia, as defined by a hemoglobin <12 g/dL in men and <11 g/dL in women, increased from 1 percent at an eGFR of 60 mL/min/1.73 m^2 to 9 percent at an eGFR of 30 mL/min/1.73 m^2 and to 33 to 67 percent at an eGFR of 15 mL/min/1.73 m^2.[c,2] Symptoms of anemia include fatigue, reduced exercise tolerance, and dyspnea. Anemia is also an all-cause mortality multiplier whereby it magnifies the risk of death from other disease states, including heart disease[3] and is associated with decreased health related quality of life.[d,4]

3.2. Description of Current Treatment Options

Decisions to treat anemia of CKD are patient specific and should include weighing the benefits and risks of various treatment options in the context of anemia-related symptoms and CKD treatment goals. Patients with anemia of CKD are first iron repleted if needed, and treated for other reversible causes of anemia i.e. vitamin B12, folate deficiencies. Erythropoiesis stimulating agents (ESAs) are injectable therapies approved for anemia of CKD that include Epogen/Procrit (epoetin alfa), Aranesp (darbepoetin alfa), Mircera (methoxy polyethylene glycol-epoetin beta) and Retacrit (epoetin alfa-epbx) and can be used after the other reversible causes of the anemia are addressed. If ESAs cannot be used or urgent correction of anemia is needed, red blood cell (RBC) transfusions are considered but are associated with

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

[d] 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.

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.[5]

4. Benefit Assessment

Four multi-center, multi-national, randomized, open-label, sponsor-blinded, active-controlled (darbepoetin) trials to support the indication proposed for vadadustat were completed, and included two trials in the NDD-CKD population (n=3476) and two in the DD-CKD population (n=3923). All four trials showed non-inferiority of vadadustat to darbepoetin in the primary efficacy endpoints as measured by the change in Hb from baseline during the primary efficacy period (maintenance period during weeks 24-36). However, both NDD-CKD and DD-CKD trial participants on vadadustat were treated with a numerically higher rates of ESA and transfusion rescues, compared to darbepoetin alfa. The increased need for ESA and transfusion rescues with vadadustat coupled with the lack of quality of life assessment in the clinical program raises concern about the overall benefit of vadadustat as the clinical reviewer references in the integrated review.[e,6]

5. Risk Assessment & Safe-Use Conditions

The pivotal trials summarized in the Benefit Assessment section comprised the safety database in addition to phase 3 trials in Japan and early phase trials. The safety population for the NDD-CKD population is composed of 3471 subjects, with 1739 subjects who received vadadustat. The safety population for the DD-CKD population is composed of 3902 subjects, 1947 subjects who received vadadustat.

5.1. MACE in the NDD-CKD Population

The adjusted pooled analyses from the pivotal trials in the NDD-CKD population failed to rule out the pre-specified risk margin of 1.25 for the primary safety endpoint of the adjudicated major adverse cardiac endpoint (MACE) outcome. The hazard ratio for adjudicated MACE with vadadustat was 1.17 (95% CI: 1.01, 1.35) compared to darbepoetin. Additional sensitivity analyses supported the increased risk of MACE with vadadustat and can be found in the integrated review.

5.2. Thromboembolic Events in DD-CKD Population

Pooled analysis of the DD-CKD pivotal trials found a clinically significant increase in adjudicated thromboembolic (TE) events in vadadustat compared to darbepoetin with a hazard ratio of 1.20 (95% CI: 0.96, 1.50). TE events were mostly in the form of venous access-related TE events.[f] Conclusions were

[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] 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.

unchanged with additional sensitivity analyses and the risk was greater when considering U.S.-only populations.

5.3. Hepatotoxicity

Review of the pooled analyses of all trials also identified a hepatotoxicity safety signal. One probable Hy's Law case was identified with vadadustat and there was a significantly higher incidence of liver injury in the vadadustat compared to darbepoetin.

6. Expected Postmarket Use

The expected prescribers are likely nephrologists and internists as well as general practitioners. Vadadustat can be given as an outpatient treatment option, instead of strictly in dialysis centers and inpatient units where ESAs are typically given. It is expected that since the vadadustat 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-CKD population.

7. Risk Management Activities Proposed by the Applicant

(b) (4)

8. Discussion of Need for a REMS

The Clinical Reviewer recommends a complete response for vadadustat on the basis of the efficacy and safety information currently available. Specifically, the increased risk of MACE and TE events relative to darbepoetin, outweighs the benefits of observed effect on Hb levels, which was reduced by higher rates of ESA and transfusion rescue.

Risk mitigation elements, such as narrowing the indicated population, minimizing the risk by early detection and reducing the negative impact of the risk once it occurred, and informed decision making were considered as possible strategies to address the risks of MACE in the NDD-CKD population and TE events in the DD-CKD population. For the risk of MACE in the NDD-CDK population, the review team has not identified a sub-population of patients where the benefits may outweigh the risk. Further, Hb is not an appropriate surrogate to monitor risk at this time because the risk was greater than with the ESA comparator at all Hb levels as evidenced by sub analysis in the US populations with lower Hb targets. MACE can be catastrophic and without warning, making an early detection strategy untenable. Negative impacts once adverse events have occurred can also not likely be reduced due to their serious and sometimes fatal nature of MACE.

For the risk of TE events in the DD-CKD population, there is no evidence in the clinical development program to suggest that the risk may be avoided or detected early to prevent worsening. The risk of thromboembolism is difficult to avoid in the DD-CKD patient population that has multiple risk factors at baseline and cannot be effectively screened for. While there are anticoagulation therapies available to treat TE events, the increased risk of thromboembolism seen in the DD-CKD cohorts is especially problematic. Access-related clots could impact patients' ability to receive required dialysis. Patients are treated after a clot is found but also potentially after it has caused a serious outcome. Further, the convenience of an oral agent is diminished since DD-CKD patients can still get their ESAs with dialysis. A strategy to ensure that healthcare providers and patients are informed of the risk of vadadustat was also considered; however, the benefit of treatment with vadadustat does not outweigh the potentially life-threatening risk of losing dialysis access or other clot-related sequelae.

At this time, the review team has not identified a sub population where the benefits may outweigh the risk and a risk management strategy that would ensure the benefits of vadadustat outweigh the risks of MACE in the NDD-CKD population and TE risks in the DD-CKD population.

9. Conclusion & Recommendations

We have evaluated all of the options for mitigating these risks and could not identify an effective strategy for mitigating the risks in the proposed populations at this time. A subpopulation where benefits may outweigh the risk of MACE in the NDD-CKD population could not be identified. There is no risk mitigation to minimize the risk, treat to lessen negative impact, or inform decision making could be identified that made the diminished benefit of vadadustat in the DD-CKD population more favorable compared to the risk of TE events and potential loss of life-saving dialysis access. We concluded that at this time a REMS would not ensure the benefits outweigh the risks for vadadustat.

10. Appendices

10.1. References

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