CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215192Orig1s000

OTHER ACTION LETTERS

NDA 215192

COMPLETE RESPONSE

Akebia Therapeutics, Inc.
Attention: Debleena Sengupta, PhD, RAC
Senior Director, Regulatory Affairs
245 First Street, Suite 1400
Cambridge, MA 02142

Dear Dr. Sengupta:

Please refer to your new drug application (NDA) dated March 28, 2021, received March 29, 2021, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for vadadustat tablets.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL AND STATISTICAL

Your submitted data do not support a favorable benefit-risk assessment of vadadustat for the proposed indication of treatment of anemia associated with chronic kidney disease (CKD) in adults not on dialysis and on dialysis. Our determination that the benefits of vadadustat do not outweigh the risks applies to both the non-dialysis-dependent (NDD) and dialysis-dependent (DD) populations of patients with anemia associated with CKD.

With regard to the benefits of vadadustat, you have met the efficacy endpoint of hemoglobin (Hb) response by demonstrating that the change from baseline in Hb with vadadustat is non-inferior to that of darbepoetin alfa, an erythropoietin stimulating agent (ESA), in both the NDD and DD populations of patients with anemia associated with CKD. However, there was higher use of rescue therapy for worsening anemia with vadadustat compared to darbepoetin alfa, particularly for ESA rescue in the NDD-CKD population and for ESA and red blood cell (RBC) transfusion rescue in the DD-CKD population. Some of these differences in rescue therapy are striking. For example, in DD-CKD Trial 0016, ESA rescue for worsening anemia was reported in 22% of vadadustat-treated patients compared to 5% of darbepoetin alfa-treated patients. The corresponding rates in DD-CKD Trial 0017 were 35% and 14%. In addition, in the DD-CKD trials there was a higher incidence of RBC transfusion rescue therapy for worsening anemia with vadadustat, which could potentially impact alloreactivity, a risk factor for renal allograft rejection in patients who undergo kidney transplantation.

As an oral therapy, vadadustat may offer convenience compared to the intravenous route of ESAs, especially in the NDD-CKD population and the minority of dialysis patients who receive peritoneal dialysis. However, the convenience of an oral drug in the DD-CKD population is less clear for most DD-CKD patients in the United States (U.S.), who receive hemodialysis and are administered ESA at the time of hemodialysis.

The trials established no other benefits of vadadustat in the NDD-CKD or DD-CKD populations.

We have identified the following major safety concerns with vadadustat that outweigh these benefits:

1. In the NDD-CKD population primary analysis, you did not establish non-inferiority for vadadustat compared to darbepoetin alfa on the primary safety endpoint of adjudicated major adverse cardiac events (MACE) – a composite of all-cause mortality, non-fatal myocardial infarction (MI) and non-fatal stroke – with a hazard ratio (HR) of 1.17 (95% confidence interval 1.01, 1.36). The upper bound of this 95% confidence interval excluded the prespecified non-inferiority margin of 1.25. Furthermore, the lower bound excluded the value of no effect. The risk of MACE with vadadustat was seen in comparison to darbepoetin alfa, an ESA with an established increased risk of non-fatal MI, non-fatal stroke, and all-cause mortality. In addition, each component of the adjudicated MACE endpoint had a numerically unfavorable HR for vadadustat compared to darbepoetin alfa.

   Your conclusion that vadadustat is safe in the U.S. population is not supported by the data. In the U.S. subgroup, the estimated hazard ratio for adjudicated MACE was 1.06 (95% CI, 0.87, 1.29); the upper bound of 1.29 does not provide assurance of an absent safety signal for MACE occurrence in the U.S. Furthermore, there was an increased hazard ratio for the non-fatal MI component of MACE in the vadadustat arm in the U.S. population (HR, 1.49, 95% CI, 0.97, 2.30), comparable to that of the overall population.

2. In the DD-CKD population, there was a concerning signal for adjudicated thromboembolic (TE) events with vadadustat compared to darbepoetin alfa, an ESA with an established increased risk of TE events. The HR was 1.20 (95% CI 0.96, 1.50) for the overall population and appeared more concerning in the U.S. subgroup, which had an estimated HR of adjudicated TE of 1.46 (95% CI 1.13, 1.89).

   Furthermore, over 80% of adjudicated TE events were vascular access thromboses. The estimated HR for adjudicated vascular access thrombosis events was 1.28 (95% CI 1.00, 1.63). This result is particularly concerning in the DD-CKD population given the critical need for vascular access for these patients.

3. Your submitted data raise concerns for a clinically significant risk for drug-induced liver injury (DILI) with the use of vadadustat in patients with CKD. This conclusion is based on one Hy's Law case, at least seven cases of probable drug-induced liver injury (DILI) with significant elevation in alanine aminotransferase (ALT) without jaundice, and an imbalance in ALT elevations with vadadustat compared to darbepoetin alfa (e.g., ALT >3x ULN in 0.47% of patients treated with vadadustat compared to 0.35% of patients treated with darbepoetin alfa; ALT >5x ULN in 0.31% of patients treated with vadadustat vs. 0.25% of patients treated with darbepoetin alfa). The elevation in alkaline phosphatase in the Hy's Law case does not preclude a conclusion of hepatocellular DILI. Using the new R-value (nR value) criterion, this subject had hepatocellular DILI with at least 10% mortality risk, fulfilling Hy's Law.

Furthermore, we have concerns that the risks seen in the clinical trials where patients were closely monitored (e.g., with liver tests), may underestimate the risks with real-world use of vadadustat, if approved. Given that ESAs are typically administered by health care providers, hemoglobin and patient monitoring is fairly well assured. With the convenience of an orally administered drug such as vadadustat, there is the potential for inadequate patient monitoring (e.g., hemoglobin, liver tests) that could lead to worse outcomes in some settings as well as the potential to prescribe vadadustat to patients with anemia and decreased creatinine clearance who presently do not receive ESAs. Some of these patients, particularly the elderly, would be at greater risk of MACE. We could not identify a risk mitigation strategy that can adequately mitigate the risks of vadadustat with the proposed dosing regimen to ensure that the benefits of vadadustat outweigh its risks.

Potential Path Forward:

1. 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. In your new clinical trial(s) also assess the following:

    - The occurrence of ESA and RBC transfusion rescue therapies, as key secondary efficacy endpoints.

    - Rhabdomyolysis as an adverse event of interest, with appropriate clinical and laboratory assessments. We noted numerical imbalances in the incidence of rhabdomyolysis, a rare event, in your NDD population (10 cases with vadadustat vs. 4 cases with darbepoetin alfa) and DD population (5 cases with vadadustat vs. 3 cases with darbepoetin alfa). Vadadustat has a known drug-drug interaction potential with some statins, but the role of this drug-drug interaction in the development of rhabdomyolysis is unclear.

    - Seizures as an adverse event of interest. The risk of seizure with vadadustat appears comparable to the known seizure risk associated with ESAs.

2. You will also need to propose and assess a strategy that successfully mitigates the risk of hepatotoxicity with the use of vadadustat in patients with CKD. Note that even if you are able to mitigate the risks of MACE and TE in a specific population or with a different dosing regimen, we have significant concerns regarding the ability to mitigate the risk of DILI given that this DILI appears idiosyncratic, and patients are not as closely monitored in the real-world setting compared to clinical trials. DILI can cause acute liver failure, the need for liver transplantation, or death. Even if rare, it is not clear that the convenience of oral dosing could outweigh such risks.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at FDA.gov.[3]

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Refer to correspondence dated, June 11, 2021, which addresses the proposed proprietary name, Vafseo. This name was found acceptable pending approval of the application in the current review cycle. Resubmit the proposed proprietary name when you respond to the application deficiencies.

---

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule
[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.

    - Present tabulations of the new safety data combined with the original application data.

    - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.

    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each subject who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

- In both the NDD-CKD population and DD-CKD populations there was a higher risk of gastrointestinal adverse reactions, including gastrointestinal acid-related disease, observed in the vadadustat arm compared to the darbepoetin alfa arm. We expect these findings to be adequately mitigated with labeling when vadadustat can be approved, provided there are no concerning gastrointestinal findings in future clinical trials of vadadustat.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Carleveva Thompson, Regulatory Project Manager, at 301-796-1403.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, MD, MMSc
Director
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HYLTON V JOFFE
03/29/2022 10:11:23 PM