

**FOOD AND DRUG ADMINISTRATION (FDA)**  
Center for Drug Evaluation and Research (CDER)

***Cardiovascular and Renal Drugs Advisory Committee (CRDAC) Meeting***

July 15, 2021

**QUESTIONS**

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The Agency has long recognized that anemia with chronic kidney disease (CKD) is a significant health burden. Anemia is a common complication of CKD that develops early in the course of the disease and worsens as CKD progresses. Currently available therapeutic options for anemia of CKD include iron, erythropoiesis stimulating agents (ESAs), and red blood cell (RBC) transfusions.

Roxadustat is a first-in-class inhibitor of hypoxia-inducible factor prolyl hydroxylases enzymes. It was hoped that the drug would achieve efficacy comparable to that of ESAs with fewer safety issues because of reduced exposure to intermittent supraphysiologic doses of erythropoietin and improved iron availability. The agent's oral route of administration is an important convenience factor for patients who are not on hemodialysis. For patients on hemodialysis, ESAs are recommended to be given by the intravenous route, and the advantage of an oral drug seems less clear.

The application provides substantial evidence of efficacy, demonstrating that roxadustat increases hemoglobin in patients who are on dialysis and not on dialysis. In the non-dialysis population, exploratory analyses show an absolute reduction in RBC transfusions of approximately 10% compared to placebo. The data show that roxadustat's efficacy is comparable to that of ESAs; however, in many cases the dosing regimen used in the trials led to overshoot of the hemoglobin target, based on mean hemoglobin responses.

The primary analyses for major adverse cardiovascular events (MACE) were neutral; however, sensitivity analyses did not favor roxadustat. Analyses of adverse events in the dialysis population demonstrated higher risks for roxadustat (versus ESAs) with respect to thrombotic events, including thrombosis of vascular access, events for which ESAs carry a Boxed Warning. Vascular access patency is crucial to perform dialysis. There was also a higher risk of seizures with roxadustat compared to ESAs, another adverse drug reaction for which there is a warning in ESA labeling.

With this background, here are the discussion points and questions:

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**QUESTIONS (cont.)**

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Non-dialysis-dependent population:

1. **DISCUSSION:** Discuss the benefits and risks of roxadustat in the non-dialysis-dependent (NDD) population.
2. **DISCUSSION:** If you have concerns regarding these risks, discuss whether you believe they could be addressed through modification of the treatment algorithm, for example, changes in target hemoglobin, starting dose, titration scheme, monitoring paradigm.
  - a. If you favor changes to the treatment algorithm to enhance safety, discuss whether they should be tested (i) prior to approval, (ii) after approval, or (iii) not at all.
3. **VOTE:** Should roxadustat be approved for the treatment of anemia due to chronic kidney disease in adult patients not on dialysis?
  - a. If not, provide your rationale, as well as recommendations for additional data and/or analyses that would support a favorable benefit-risk profile and approval of roxadustat.

Dialysis-dependent population:

4. **DISCUSSION:** Discuss the benefits and risks of roxadustat in the dialysis-dependent (DD) population.
5. **DISCUSSION:** If you have concerns regarding these risks, discuss whether you believe they could be addressed through modification of the treatment algorithm, for example, changes in target hemoglobin, starting dose, titration scheme, monitoring paradigm.
  - a. If you favor changes to the treatment algorithm to enhance safety, discuss whether they should be tested (i) prior to approval, (ii) after approval, or (iii) not at all.
6. **VOTE:** Should roxadustat be approved for the treatment of anemia due to CKD in adult patients on dialysis?
  - a. If not, provide your rationale, as well as recommendations for additional data and/or analyses that would support a favorable benefit-risk profile and approval of roxadustat.