Testimony Before the FDA's Cardiovascular and Renal Drugs Advisory Committee Meeting: Daprodustat Offers No Clinical Benefits But Increases Risks For Chronic Kidney Disease Patients

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I am Nina Zeldes, a Health Researcher at Public Citizen's Health Research Group. I have no financial conflict of interest.

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Public Citizen strongly opposes Food and Drug Administration (FDA) approval of daprodustat for the treatment of anemia due to chronic kidney disease (CKD), both in adult patients not on dialysis and those on dialysis.

As detailed in the FDA review,[1] this drug offers no additional benefits compared to erythropoiesis-stimulating agents (ESAs), the currently available FDA-approved treatment options, while putting patients at substantial additional safety risks.

ESAs already carry a black-box warning because of an increased mortality risk for patients, as well as an increased risk for adverse events such as stroke and myocardial infarction. We thus agree with the FDA that any further increase in risks "beyond that seen with the ESAs is concerning."[2]

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In the pivotal trials in patients not on dialysis and those on dialysis, daprodustat was noninferior to ESAs regarding the change in the hemoglobin level from baseline. The need for red blood cell transfusions or rescue therapy was also similar between the treatment arms, and, as stated by the FDA "there were no other benefits demonstrated on how patients feel, function, or survive."[3]

In contrast to the lack of clear clinical benefit relative to current treatment with ESAs, both trials demonstrated that this drug has serious additional safety risks for patients.

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[1] Food and Drug Administration. FDA briefing document, NDA 216951, drug name: daprodustat; Cardiovascular and Renal Drugs Advisory Committee Meeting. October 26, 2022. https://www.fda.gov/media/162521/download. Accessed October 26, 2022.
[2] *Id*. PDF p. 8.
[3] *Id*. PDF p. 7.

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Patients taking daprodustat in both trials had a higher incidence of hospitalizations for heart failure and bleeding gastric erosions.

For example, the hazard ratio for hospitalization for heart failure for non-dialysis patients was 1.22 (95% confidence interval [CI] 0.95, 1.56) and 1.10 (95% CI 0.84, 1.45) for patients on dialysis, and patients with a history of heart failure were at higher risk.[4] The hazard ratio for serious gastric erosion events, the risk of which seemed to accumulate constantly over time, was 1.96 (95% CI 1.24, 3.09) in non-dialysis patients and 1.16 (95% CI 0.78, 1.73) for those on dialysis.[5]

In general, the risks of this drug for patients not on dialysis are particularly concerning. The data showed this group, especially in the USA subgroup, had increased risk estimates for several cardiovascular outcomes including cardiovascular mortality, myocardial infarction, stroke, thromboembolic disease, and vascular access thrombosis. Patients also had elevated hazard ratios for major adverse cardiovascular events (MACE) in some analyses, and potentially increased risk for acute kidney injury.[6]

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The elevated hazard ratios for cardiovascular outcomes are particularly concerning as the incidence across all cardiovascular outcomes, except for stroke, was higher in the USA subgroup, as can be seen here in Figure 5 of the FDA review.[7] For example, in the daprodustat group the incidence rate of thromboembolic events was 3.1 per 100 patient years (PY), compared to 1.5 in the ESA group, a hazard ratio of 2.03 (95% CI 1.06, 3.87). The hazard ratio for cardiovascular mortality was similarly increased at 1.86 (95% CI 1.10, 3.12), where the incidence rate was 4.4 per 100 PY for daprodustat compared to 2.4 in the ESA arm.[8]

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FDA's analysis of treatment-emergent serious adverse events also showed that 4.9% of patients not on dialysis taking the new drug had acute kidney injury compared to 3.3% in the ESA group with a relative risk of 1.5 (95% CI 1.1, 2.0).[9] The cumulative incidence at years 2 and 3 are shown here in Figure 8 of the FDA review.[10]

[4] *Id*. PDF p. 37.
[5] *Id*. PDF pp. 39-40.
[6] *Id*. PDF p. 8.
[7] *Id*. PDF pp. 36-37.
[8] *Ibid*.
[9] *Id.* PDF p. 52.
[10] *Id.* PDF p. 41.

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In conclusion, this drug has serious additional safety risks for patients, particularly those not on dialysis and offers no additional clinical benefits for patients. The oral route, while offering convenience, also appears to put patients at a higher risk for serious harm.

In fact, this pattern of increased safety risks compared to ESAs seems to be a concern of drugs of this class, and a similar drug, roxadustat, was not recommended for approval over similar concerns earlier this year.[11]

We therefore urge the committee to vote "No" on the two voting questions and recommend that the FDA not approve daprodustat.

[11] Public Citizen. Comments submitted to Docket No. FDA-2021-N-0441 for the Cardiovascular and Renal Drugs Advisory Committee Meeting on July 15, 2021. https://www.citizen.org/wp-content/uploads/2595.pdf. Accessed October 26, 2022.