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Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Comments Submitted to Docket No. FDA-2021-N-0441 for the Cardiovascular and Renal Drugs Advisory Committee Meeting on July 15, 2021; Notice of Meeting; Establishment of a Public Docket; Request for Comments

Sidney Wolfe M.D., Public Citizen's Health Research Group

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, submits these comments to the Food and Drugs Administration (FDA) regarding the new drug application (NDA) 213805 for roxadustat, an oral film-coated tablet submitted by FibroGen, Inc. The proposed indication is for the treatment of anemia due to chronic kidney disease (CKD) in adult patients not on dialysis and on dialysis.

The most serious public health concern if roxadustat is approved will be that a drug with no truly unique benefits, but some known increased risks compared to earlier FDA-approved erythropoiesis-stimulating agents (ESAs), will become widely available.

According to the FDA, roxadustat's efficacy is comparable to that of ESAs. However, there are important increased risks of serious thromboembolic events, as well as other serious adverse event, with roxadustat compared with ESAs.

The FDA conducted exploratory analyses to elucidate associations between thromboembolic events and roxadustat dose, hemoglobin (Hb) concentrations, and Hb rates of rise and decline, and found that higher rates of Hb rise (and decline) were associated with higher rates of thromboembolic events. The FDA noted in its review that "In light of these findings, the applicant [FibroGen] speculates that thromboembolic risks might be reduced through use of a lower roxadustat starting dose. Their prediction seems plausible but is unproven."[1] This concern

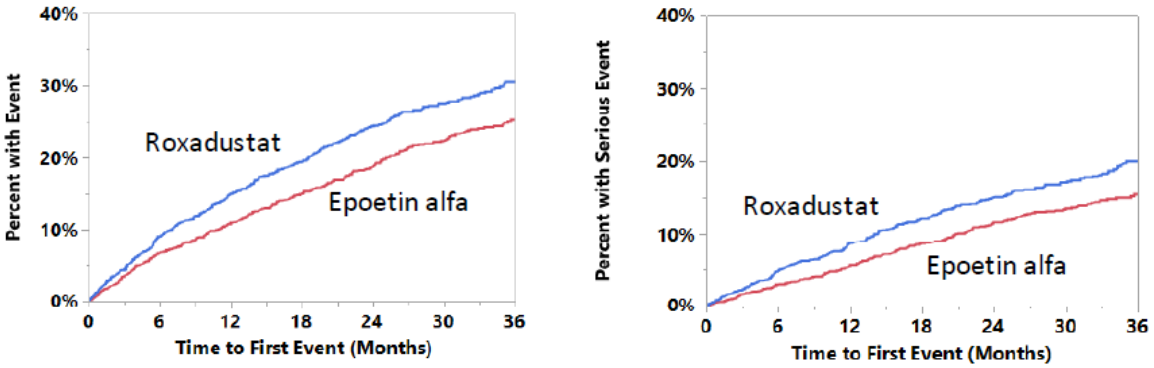
[1] Food and Drug Administration. FDA briefing document, Cardiovascular and Renal Drugs Advisory Committee Meeting, July 15, 2021, Roxadustat. https://www.fda.gov/media/150728/download. Accessed July 14, 2021. PDF page 12.

about an unproven dose-lowering remedy for the increased risk of thromboembolic events applies to both dialysis dependent (DD) and non-dialysis dependent (NDD) patients.

In DD study 613, the relative risks of congestive heart failure and arteriovenous fistula thrombosis in subjects treated with roxadustat compared with those treated with an ESA were both 2.0. Commenting on these findings, the FDA noted that "thrombosis of vascular access is listed as an adverse drug reaction in the ESA labeling (as a warning). The risk of congestive heart failure is also listed as an adverse drug reaction when ESAs are used to target excessive Hb concentrations. Thus, these signals from Study 613 are quite concerning (both with a relative risk of 2 vs. ESAs), because they suggest that roxadustat's risks are even greater than those of ESAs."[2]

Because of the importance of thromboembolic events, the FDA performed a Kaplan-Meier time-to-first thrombotic event analysis for the three pivotal trials conducted in the DD subject population (Figure 22, excerpted below) for all (left) and serious (right) events.[3]

Figure 22: Time to First Thrombotic Event—All Events (Left); Serious Events (Right) for the DD Population (Studies 002, 063, and 064); OT+7 Ascertainment Window



Source: FDA analysis

The FDA noted that the excess thrombotic risk of roxadustat compared to epoetin alpha "accrues continuously throughout the three studies."[4] There are much more risk data from the DD trials, since all involved a positive comparator, but even in the only NDD trial with an ESA comparator group, study 610, concerns were identified about increased risks of serious adverse events with roxadustat compared with the ESA.[5]

Even if only approved for NDD patients, it is likely, if not certain, that the risks of harm will be even more than found in study 610. Whereas DD patients on dialysis are frequently monitored,

[2] *Ibid*. PDF page 42.
[3] *Ibid*. PDF page 65.
[4] *Ibid*. PDF page 65.
[5] *Ibid*. PDF page 38.

many NDD patients will be followed much less often than in the clinical trials, bolstered by the myth that the FDA would not have approved the drug if it were not safe enough for them.

We therefore strongly oppose the approval of roxadustat for any patients.