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Testimony Before the Food and Drug Administration's Cardiovascular and Renal Drugs Advisory Committee: The FDA Must Reject New Drug Application #215484 for Bardoxolone Methyl for Slowing the Progression of Chronic Kidney Disease Caused by Alport Syndrome

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December 8, 2021

I am Dr. Michael Carome, Director of Public Citizen's Health Research Group, and previously was a practicing board certified nephrologist for nearly two decades. I have no financial conflicts of interest.

Public Citizen strongly opposes approval of bardoxolone methyl because the drug has well-established risks of serious harms but the CARDINAL phase 3 trial failed to provide substantial evidence that the drug slows the progression of chronic kidney disease (CKD) in Alport syndrome (AS) patients. As a result, a favorable benefit-risk profile has not been established for bardoxolone.

Importantly, bardoxolone causes a myriad of diverse biological effects in multiple organs, the mechanisms and implications of which are not well-understood in many cases.

Safety concerns

Combined safety data from the CARDINAL phase 3 trial in AS subjects[1] and the BEACON trial[2] in subjects with type 2 diabetes and CKD revealed that bardoxolone was associated with a higher incidence of the following adverse effects, among others:

- Heart failure
- Increased blood pressure (systolic and diastolic)
- Increased proteinuria
- Weight loss
- Decreased appetite, dysgeusia, nausea, and vomiting
- Anemia
- Hypomagnesemia
- Muscle spasms

[1] Food and Drug Administration. FDA briefing document for Cardiovascular and Renal Drugs Advisory Committee meeting. December 8, 2021. https://www.fda.gov/media/154630/download. Accessed December 7, 2021. PDF pages 26-34.
[2] de Zeeuw S, Akizawa R, Audhya P, et al. Bardoxolone methyl in type 2 diabetes and stage 4 chronic kidney disease. *N Engl J Med*. 2013 Dec 26;369(26):2492-2503.

Increases in blood pressure and proteinuria are factors that likely augment the risks of adverse cardiovascular and renal outcomes.

Notably, the BEACON trial was terminated early after 2,185 subjects had been enrolled with median follow-up of 9 months because of excess serious adverse events in bardoxolone-group subjects, including hospitalization or death due to heart failure, cardiovascular death, and a composite endpoint of nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or cardiovascular death.[3]

The CARDINAL phase 3 trial, which enrolled only 157 subjects,[4] was too small to detect any differences in important cardiovascular outcomes.

Lack of substantial evidence of benefit

Given bardoxolone's troubling safety profile, approval of the drug would only be justifiable if there was robust evidence that the drug provides substantial clinical benefit. However, as Food and Drug Administration (FDA) reviewers explain in detail, the CARDINAL phase 3 trial data failed to demonstrate that bardoxolone is effective in slowing the loss of kidney function in patients with AS and reducing the risk of progression to kidney failure. In particular, the statistically significant effects seen with bardoxolone on the primary and key secondary endpoints likely were largely due to reversible pharmacodynamic (PD) treatment effects of bardoxolone.[5] FDA reviewers convincingly argue that the duration of the four-week washout periods in the CARDINAL phase 3 trial was insufficient to resolve the reversible PD effect of bardoxolone.

Conclusions

In closing, given the lack of substantial evidence of effectiveness and clear risks of serious harms, Public Citizen urges your committee vote to "no" on question 4 (Does the provided evidence demonstrate that bardoxolone methyl is effective in slowing the progression of chronic kidney disease in Alport syndrome and that its benefits outweigh its risks?) and to recommend that the FDA not approve bardoxolone.

[3] *Ibid*.
[4] Food and Drug Administration. FDA briefing document for Cardiovascular and Renal Drugs Advisory Committee meeting. December 8, 2021. https://www.fda.gov/media/154630/download. Accessed December 7, 2021. PDF page 9.
[5] *Ibid*. PDF pages 15-26 and 44-64.