Testimony Before the FDA's Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Peripheral and Central Nervous System Drugs Advisory Committee Meeting Regarding Brexpiprazole

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Slide 1

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

Slide 2

Public Citizen strongly opposes FDA approval of brexpiprazole for the treatment of agitation in patients with Alzheimer's disease because:

1) this drug's small benefit does not outweigh the significant risks, and
2) due to the limitations of the provided data, a population for which the benefits outweigh the risks cannot be identified.

Slide 3

The evidence regarding efficacy is based on three studies of which only two reached statistical significance over placebo for the primary endpoint.[1]

Moreover, in the 1 milligram (mg) or 2 mg fixed dose study (study 331-12-283), statistical significance was only reached in the 2 mg group. The treatment difference on a score that ranges from 29 to 203 points was -3.77 (95% confidence interval [CI] -7.38, -0.17, p-value = 0.0404),[2] a result that FDA did not consider "statistically persuasive."[3]

The flexible dose study did not reach statistical significance (study 331-12-284).[4] While the combined treatment difference of -5.32 (95% CI −8.77, −1.87, p = 0.0026) in the 2 mg or 3 mg fixed dose study (study 331-14-213) was statistically significant, additional

[1] Food and Drug Administration. FDA briefing document, NDA 205422/S-009, drug name: brexpiprazole; Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Peripheral and Central Nervous System. April 14, 2023. https://www.fda.gov/media/167066/download. Accessed April 14, 2023.
[2] *Id.* PDF p. 18.
[3] *Id.* PDF p. 11.
[4] *Id.* PDF p. 23.

analysis showed that for the secondary endpoint, only the 3 mg group reached statistical significance.[5]

Based on these results, we disagree with the FDA's assessment that there is substantial evidence of effectiveness.[6]

Slide 4

These limited benefits stand in opposition to serious safety concerns. For instance, common adverse events in subjects treated with this drug included urinary tract infection, somnolence, and insomnia. Subjects in the treatment arm generally also had a higher incidence of adverse events of special interest, such as cardiovascular events.[7]

Slide 5

Of particular concern, however, is the almost five times higher mortality risk (estimated incidence rate ratio relative to placebo 4.75, 95% CI 0.59, 38.08),[8] a risk that FDA noted "follows a similar trend with the mortality risk estimated for other antipsychotics," as shown in Figure 4 of the briefing materials.[9]

Slide 6

Across all 3 studies subjects were relatively young (mean 74 years of age), had a low rate of comorbid psychiatric symptoms (between 19 – 26%) and were predominantly White (95%).[10]

Based on the provided evidence, no patient group that would benefit from this drug was identified. Moreover, the dosing of brexpiprazole at 3 mg was only explored in one of the three studies.

Slide 7

In conclusion, there is not sufficient data to identify a population for whom the benefits outweigh the significant risks. Instead, like other antipsychotics used in elderly patients with dementia-related psychosis, this is a drug that can kill patients without providing a meaningful benefit.

We therefore urge the committee to vote "No" on the voting question and strongly recommend that the FDA not approve brexpiprazole for the treatment of agitation in patients with Alzheimer's disease.

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[5] *Id.* PDF p. 29-30.
[6] *Id.* PDF p. 31.
[7] *Id.* PDF p. 55.
[8] *Id.* PDF p. 33.
[9] *Id.* PDF p. 34.
[10] *Id.* PDF p. 19, 22-23, 28-29.