May 3, 2023

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Re: Supplemental New Drug Application 205422/S-009 for brexpiprazole for the treatment of agitation associated with Alzheimer's dementia

Dear Drs. Califf, Cavazzoni, and Farchione,

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, is writing to strongly urge the Food and Drug Administration (FDA) to reject the supplemental new drug application (NDA) 205422/S-009, submitted by Otsuka Pharmaceutical Company Ltd. and Lundbeck Inc., for brexpiprazole for the treatment of agitation associated with Alzheimer's dementia (AAD). Brexpiprazole was the subject of the April 14, 2023, joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Peripheral and Central Nervous System Drugs Advisory Committee (the Committees).[1] This

[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 May 3, 2023.

letter supplements Public Citizen's testimony presented at that meeting during the open public hearing. [2]

As noted in our testimony, we oppose approval of this drug for this additional indication because its small benefit does not outweigh its significant risks and because no population for which the benefits would outweigh the risks was identified. However, we are particularly concerned that these issues, which the FDA specifically requested the Committees to consider, were neither adequately addressed by the FDA before or during the meeting nor discussed in depth by the Committees.[3] We believe that the lack of robust discussion of these serious concerns is partially responsible for the almost unanimous agreement (nine yeses, one no, zero abstentions) of the Committees on the voting question that "the Applicant provided sufficient data to allow identification of a population in whom the benefits of treating agitation associated with Alzheimer's dementia with brexpiprazole outweigh its risks"[4] despite the many open questions, as discussed below.

Overall benefit/risk assessment

Although the FDA noted that the applicant provided "substantial" evidence of effectiveness,[5] we disagree with this assessment: The benefit demonstrated was weak and based on three studies of which only two reached statistical significance over placebo for the primary endpoint.

For instance, 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. More importantly, the mean group treatment difference on a score that ranges from 29 to 203 points was just -3.77 (95% confidence interval [CI] -7.38, -0.17, p-value = 0.0404).[6] This amounts to a 2.2% difference that is unlikely to be clinically meaningful and that the FDA itself did not consider "statistically persuasive."[7]

The group difference on the primary efficacy outcome for the flexible-dose (individual titration, 0.5 to 2 mg) study did not reach statistical significance (study 331-12-284).[8] Although a separate study (331-14-213) found that the combined treatment difference of -5.32 (95% CI −8.77, −1.87, p = 0.0026) for the 2-mg or 3-mg fixed dose was statistically significant regarding the primary outcome of "agitation inventory" score, additional analysis showed that for the important

[2] Public Citizen. Testimony before the FDA's joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Peripheral and Central Nervous System Drugs Advisory Committee regarding brexpiprazole. April 14, 2023. https://www.citizen.org/article/testimony-before-the-fdas-joint-meeting-of-the-psychopharmacologic-drugs-advisory-committee-and-the-peripheral-and-central-nervous-system-drugs-advisory-committee-regarding-brexpiprazole/. Accessed May 3, 2023.
[3] Food and Drug Administration. April 14, 2023, joint meeting of the PDAC and the PCNS. https://www.youtube.com/watch?v=ifsdFhLg0Cg. Accessed May 3,2023.
[4] Food and Drug Administration. Joint meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC) and the Peripheral and Central Nervous System Drugs Advisory Committee (PCNS). Questions. April 14, 2023. https://www.fda.gov/media/167128/download. Accessed May 3, 2023.
[5] 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 May 3, 2023
[6] *Id.* PDF p. 18.
[7] *Id.* PDF p. 11.
[8] *Id.* PDF p. 23.

secondary endpoint of "clinical global impression-severity" score, the analogous therapeutic effect was distinctively less certain, with only the 3-mg group reaching statistical significance.[9]

Moreover, the clinical meaningfulness of any of these results for patients and caregivers as well as possible long-term harms were not adequately scrutinized by the FDA or the Committees.

These small benefits stand in stark contrast to **the higher mortality risk**.[10] In fact, like all antipsychotics, brexpiprazole already has a black-box warning because of the increased risk of death among elderly patients with dementia, and as noted by the FDA, "brexpiprazole's effect on mortality appears to be consistent with the known risk with other antipsychotics in elderly patients with dementia."[11] Moreover, common adverse events in subjects treated with this drug included urinary tract infection, somnolence, and insomnia, and subjects in the treatment arm generally also had a higher incidence of adverse events of "special interest," such as cardiovascular events.[12]

Based on these data it thus seems clear that brexpiprazole, like other antipsychotics, is a drug that does not provide a meaningful benefit while putting patients at an increased risk of harm.

Is there a population for whom the benefit/risk profile appears acceptable?

Even though the FDA requested that the Committees "discuss whether there is a population of patients with Alzheimer's dementia for whom the benefit/risk of brexpiprazole appears acceptable,"[13] the Committees did not converge on any clear characterization of which patients benefit from this medication because very little data was presented by the FDA that shed light on this critical question of "indicated population." As a result, the Committees were unable to agree on whether patients with more mild or more severe symptoms were most likely to benefit.[14] More concerning, however, is that **despite acknowledging this lack of data,** the Committees overwhelmingly voted "yes" when asked whether sufficient data were provided.

But if a determination of a specific population for whom the benefit/risk profile is acceptable is not possible based on the available data, it is reasonable to assume that this drug will be excessively prescribed, often long-term, for most AAD patients, putting them at unnecessary risk with limited or no clinically meaningful benefit. Accordingly, an approval of AAD as an additional indication for brexpiprazole would — ironically — run in direct opposition to one of the few existing and agreed-upon quality-of-care indicators for long-term care facilities in the United States.[15]

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[9] *Id.* PDF p. 29-30.
[10] *Id.* PDF p. 33.
[11] *Id.* PDF p. 6.
[12] *Id.* PDF p. 55.
[13] Food and Drug Administration. Joint meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC) and the Peripheral and Central Nervous System Drugs Advisory Committee (PCNS). Questions. April 14, 2023. https://www.fda.gov/media/167128/download. Accessed May 3, 2023.
[14] Food and Drug Administration. April 14, 2023 Joint meeting of the PDAC and the PCNS. https://www.youtube.com/watch?v=ifsdFhLg0Cg. Accessed April 28,2023.
[15] Burgess JG, Maust DT, Myron Chang MU, et al. Identifying quality indicators for nursing home residents with dementia: A modified Delphi method. *J Geriatr Psychiatry Neurol*. 2023;36(2):164-170.

Indeed, based on a *New York Times* investigation,[16] we already know that at least 21% of residents in nursing homes are given antipsychotic drugs to control behavioral problems and that some nursing homes are hiding the true extent to which their residents are being irresponsibly prescribed sedating and potentially deadly antipsychotic drugs.[17] If brexpiprazole were approved, it seems clear this inappropriate use of dangerous antipsychotic drugs will only be exacerbated.

Conclusion

Although we agree that AAD is an unmet need that can be extremely challenging for patients and their caregivers, it seems clear based on the provided data that brexpiprazole does not meet this need. In addition, the FDA and the Committees failed to address the serious concerns outlined above in adequate depth or breadth to assure patients, caregivers, and prescribers that there is a specific patient group that would benefit from this drug, especially given the increased mortality risk of antipsychotic drugs.

Patients and caregivers deserve better: They need to be able to trust that a drug approved by the FDA for AAD has an acceptable safety profile and has demonstrated consistent, significant, and meaningful benefits. If the FDA nevertheless approves brexpiprazole, it will provide false hope to the large number of desperate families of patients with Alzheimer's dementia.

We thus strongly urge the FDA not to approve this additional label indication for brexpiprazole.

Thank you for your attention to this important matter.

Sincerely,

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[16] Thomas, K., Gebeloff, R., Silver-Greenberg, J. Phony diagnoses hide high rates of drugging at nursing homes. *The New York Times*. Updated October 15, 2021. https://www.nytimes.com/2021/09/11/health/nursing-homes-schizophrenia-antipsychotics.html. Accessed May 3, 2023.
[17] Public Citizen. Outrage of the month: Nursing homes, U.S. government hide misprescribing of antipsychotic drugs to elderly dementia patients. *Health Letter*. October 2021.https://www.citizen.org/article/outrage-of-the-month-nursing-homes-u-s-government-hide-misprescribing-of-antipsychotic-drugs-to-elderly-dementia-patients/. Accessed, May 3, 2023.

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