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

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I have no financial conflicts of interest.

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Introduction

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

1) **The small benefit of brexpiprazole does not outweigh the significant risks.**
2) **Due to the limitations of the provided data a population for which the benefits outweigh the risks cannot be identified.**

Evidence for Efficacy

Study 331-12-283 (1 mg or 2 mg daily)

- **Statistical significance of primary endpoint reached only in 2 mg group**
- **treatment difference of -3.77 (on a score that ranges from 29 to 203)**
- **FDA did not consider these results to be "statistically persuasive"**

Study 331-12-284 (0.5 mg – 2 mg daily)

- **Statistical significance was not reached for primary endpoint**

Study 331-14-213 (2 mg or 3 mg daily)

- **Statistical significance of primary endpoint reached for the combined 2 mg and 3 mg group**
- **Treatment difference –5.32 (on a score that ranges from 29 to 203)**
- **Additional analysis showed that secondary endpoint significant only for 3 mg group**

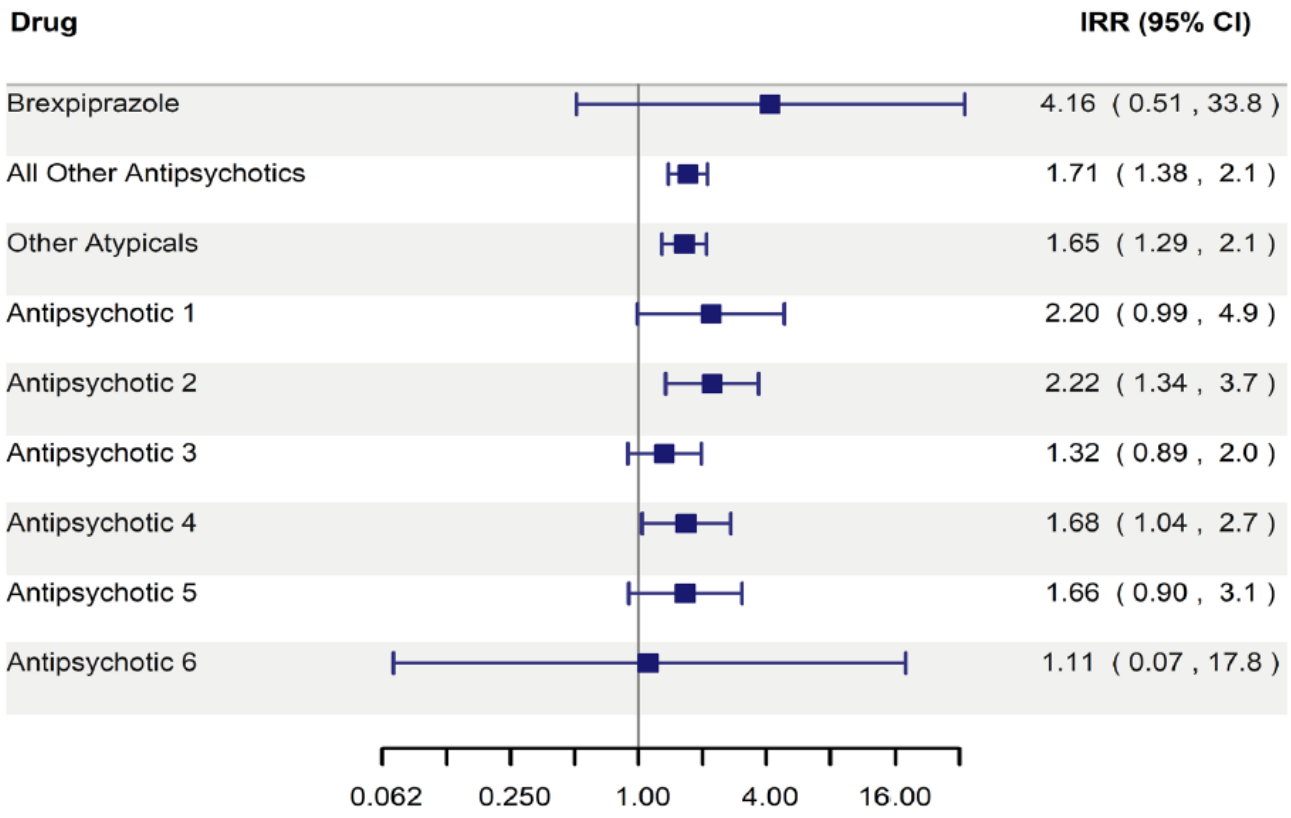
-> Based on these studies, there is not substantial evidence of effectiveness

Safety Considerations

- Adverse events such as urinary tract infections, somnolence and insomnia were higher in the subjects treated with brexpiprazole
- Patients treated with brexpiprazole had a generally higher incidence of adverse events of special interest, e.g. cardiovascular events
- Higher mortality risk in the brexpiprazole group vs placebo group (8 subjects [1.2% of subjects, N=655] vs 1 subject [0.26%, N=388], respectively)

Mortality Risk for Brexpiprazole

Figure 4: Comparison of Brexpiprazole's Mortality Risk versus FDA's Previous Findings (Deaths Observed in the Intended Period of Observation + 30 Days Follow-Up Sampling Time Frame)



Source: Reviewer-created using adae.xpt dataset and the Agency's internal review document authored by Dr. Marc Stone
Abbreviations: CI = confidence interval; IRR = incident rate ratio (referred to as mortality risk)
Note: "All other antipsychotics" and "other atypicals" groups do not include brexpiprazole.

Generalizability of Data

- **Subjects were relatively young (mean 74), predominantly White (95%) and had a low rate of comorbid psychiatric symptoms (19-26%)**

- **No patient group for which the benefits of brexpiprazole would outweigh the risks was identified**

- **The dosing of brexpiprazole at 3 mg was only explored in one of the three studies discussed**

Conclusion

- **The small benefits do not outweigh serious safety concerns**
- **There is not sufficient data to allow identification of a population in whom the benefits of this drug outweigh its risks**

-> We therefore urge the committee to vote “No” on the voting question and strongly recommend that the FDA not approve brexpiprazole.