

April 13, 2023

Joyce Frimpong, PharmD
Designated Federal Officer
Division of Advisory Committee and Consultant Management
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: FDA–2023–N–0985, April 14, 2023, Meeting of the Psychopharmacologic Drugs Advisory Committee and the Peripheral and Central Nervous System Drugs Advisory Committee

Dear Dr. Frimpong and members of the Psychopharmacologic Drugs Advisory Committee and the Peripheral and Central Nervous System Drugs Advisory Committee,

While signatories to this public comment letter do not take a position on the merits of the application for FDA approval of brexpiprazole for agitation associated with Alzheimer’s disease (AAD), we write to urge the Advisory Committees to consider the perspectives of people living with Alzheimer’s disease, family and other care partners, long-term care and health care providers, and advocates as you discuss proposed expansion of the brexpiprazole label.

Although prevalence estimates vary, a March 2023 *International Psychogeriatrics* article notes that “agitated behavior occurs in up to 70% of patients in the course of AD dementia and is more likely to occur in patients with more severe cognitive impairment.”¹ In addition to AAD, other emotional and mood changes, also known as neuropsychiatric symptoms (NPS), frequently occur with Alzheimer’s disease and can include aggression, anxiety, sleep problems, depression, psychosis, and apathy.² The presence of NPS in people with Alzheimer’s disease may worsen other clinical outcomes, leading to higher rates of cognitive and functional decline, earlier time to institutionalization, and earlier death.³

It is important to note that the regulatory issue before this committee is to provide advice and recommendation on a *supplemental new drug application (sNDA) for a drug that already has an approved new drug application*. Brexpiprazole is an atypical antipsychotic medication that was approved by the FDA in 2015 for the treatment of schizophrenia and as adjunctive therapy for major depressive disorder (MDD). A published 2023 analysis of the safety, efficacy, and tolerability of brexpiprazole in patients with agitation in Alzheimer’s dementia found statistically significantly greater

¹ Cummings, J., et al (2023). *Reduction and prevention of agitation in persons with neurocognitive disorders: An international psychogeriatric association consensus algorithm*. *International Psychogeriatrics*, 1-12.

² Van Dam D, et al. *Neuropsychiatric Disturbances in Alzheimer's Disease: What Have We Learned from Neuropathological Studies?* *Curr Alzheimer Res*. 2016;13(10):1145-64.

³ Lanctot KL, et al.: *Neuropsychiatric signs and symptoms of Alzheimer’s disease: new treatment paradigms*. *Alzheimers Dement (N Y)* 2017; 3:440–449

improvements in agitation versus placebo, supporting the findings of two prior clinical trials. Brexpiprazole was well tolerated, which is of particular importance in this vulnerable patient population.⁴ This sNDA follows eight years of accumulated safety and efficacy data on the original NDA.

We have full confidence in the FDA staff and leadership’s analyses and recommendations regarding whether an expansion of the label for brexpiprazole is supported based on the agency’s comprehensive review of the clinical trial data.

Substantial unmet clinical need

At the time of writing, only two drugs have been approved by the FDA on the basis of being reasonably likely to indicate slowing the progression of Alzheimer’s disease based on clearing of beta-amyloid plaques, while other medications are undergoing Phase III trials. These drugs are intended for patients with mild cognitive impairment or mild dementia due to Alzheimer’s disease. Despite the hope provided by these advances, for patients that progress to moderate or severe dementia due to Alzheimer’s disease, additional supports can help manage AAD and other neuropsychiatric symptoms. Currently there is no Food and Drug Administration (FDA) approved medication for the on-label treatment of AAD.

In 2015, the International Psychogeriatric Association (IPA) published a provisional consensus definition of agitation in cognitive disorders—including AAD.⁵ Individuals with AAD may experience excessive motor activity (e.g., pacing, rocking, gesturing, pointing fingers, restlessness, performing repetitious mannerisms); verbal aggression (e.g. yelling, speaking in an excessively loud voice, using profanity, screaming, shouting); and/or physical aggression (e.g. grabbing, shoving, pushing, resisting, hitting others, kicking objects or people, scratching, biting, throwing objects, hitting self, slamming doors, tearing things, and destroying property)—with behaviors severe enough to cause significant impairment in interpersonal relationships, other aspects of social functioning, or in the person’s daily living activities. In March 2023 validation and use of the IPA definition was summarized and the word “provisional” was removed.⁶ That same month, the IPA Agitation Workgroup developed an agitation assessment and treatment algorithm aimed at reducing or preventing the recurrence of agitation in individuals with cognitive impairment. The algorithm presents specific strategies to evaluate agitation, determine its possible causes, formulate psychosocial interventions, identify pharmacologic treatment if appropriate for the circumstances, assess the success of the interventions, and seek ways to prevent potentially recurrent agitation.⁷

⁴ Grossberg G, et al. *Efficacy, Safety and Tolerability of Brexpiprazole for the Treatment of Agitation in Alzheimer’s Dementia: A 12-Week, Randomized, Double-Blind, Placebo-Controlled Trial*. The American Journal of Geriatric Psychiatry. Volume 31, Issue 3, Supplement, 2023, Pages S99-S100.

⁵ Cummings J, et al. *International Psychogeriatric Association. Agitation in cognitive disorders: International Psychogeriatric Association provisional consensus clinical and research definition*. Int Psychogeriatr. 2015 Jan;27(1):7-17..

⁶ Sano, M., et al. (2023). *Agitation in cognitive disorders: Progress in the International Psychogeriatric Association consensus clinical and research definition*. International Psychogeriatrics, 1-13.

⁷ Cummings, J., et al. (2023). *Reduction and prevention of agitation in persons with neurocognitive disorders: An international psychogeriatric association consensus algorithm*. International Psychogeriatrics, 1-12.

Barriers to meeting clinical need

Non-pharmacologic and pharmacologic interventions may be considered in the treatment of AAD.⁸ Clinical guidelines and patient groups support first-use of non-pharmacologic and environmental interventions.^{9,10} At the same time, an August 2020 final systematic evidence review by AHRQ of non-pharmacologic interventions found, “Despite hundreds of studies, very little evidence supports widespread dissemination of any general care approaches for PLWD [people living with dementia] or caregivers. This review demonstrates the need for larger, longer-term, and more-rigorous studies of interventions.”¹¹ For patients for whom it is clinically indicated and medically appropriate given the severity or distress induced by agitation or aggressiveness, access to antipsychotics can lower the incidence of symptoms and improve quality of life.

Misconceptions around cause of increased mortality in patients with dementia

In 2005 the FDA instituted a “boxed” warning for second-generation antipsychotic medications after a meta-analysis of randomized controlled trials found these agents were associated with a small increase in risk for death in patients with Alzheimer’s disease;¹² in 2008 a similar warning was added to the labels of first-generation antipsychotics. However, subsequent published reviews have found that *it is neuropsychiatric symptom progression that increases the risk of death in older people with dementia*. A large longitudinal observational study published in the September 2013 issue of the *American Journal of Psychiatry* showed that the primary correlation of adverse outcomes was the psychiatric symptomatology of dementia progression and not a result of the drugs used to treat the condition.¹³ It is important for the FDA to recognize that Alzheimer’s is a progressive and fatal disease, and we encourage the agency to reexamine its 2005 boxed warning.

Absence of drugs with an on-label indication for treatment of neuropsychiatric symptoms in Alzheimer’s disease

Currently, antipsychotics are used on an off-label basis to manage systems for people with ADP.¹⁴ While clinical guidelines may support use for specific patient populations, the lack of on-label

⁸ Reus, VI., et al. *The American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients with Dementia*. American Journal of Psychiatry. 1 May 2016.

⁹ Ibid.

¹⁰ Alzheimer’s Association. *Challenging Behaviors*. Sept 2011. https://www.alz.org/national/documents/statements_antipsychotics.pdf

¹¹ Butler M, et al. *Care Interventions for People Living with Dementia and Their Caregivers. Comparative Effectiveness Review No. 231*. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2015-00008-I.) AHRQ Publication No. 20-EHC023. Rockville, MD: Agency for Healthcare Research and Quality; August 2020. Posted final reports are located on the Effective Health Care Program search page. DOI: <https://doi.org/10.23970/AHRQEPCCER231>.

¹² Schneider LS, et al. *Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials*. JAMA 2005; 294:1934–1943 Crossref, Medline, Google Scholar

¹³ Lopez OL, et al. *The long-term effects of conventional and atypical antipsychotics in patients with probable Alzheimer’s disease*. Am J Psychiatry 2013; 170:1051–1058.

¹⁴ Maher, AR., et al. *Efficacy and Comparative Effectiveness of Atypical Antipsychotic Medications for Off-Label Uses in Adults: A Systematic Review and Meta-analysis*. JAMA 306:12. 28 Sept 2011. <https://jamanetwork.com/journals/jama/fullarticle/1104423>

prescriptions presents potential access issues – most prominently, whether health insurance will provide reimbursement for treatment with the drug for AAD. When there is appropriate evidence, sponsors should seek out FDA approval for indications to alleviate these barriers, and FDA should add indications when evidence related to approved endpoints indicates significance over placebo and/or existing treatment patterns.

Conclusion

We thank the FDA and the Advisory Committees for the opportunity to share our feedback during this review. For people facing agitation associated with Alzheimer’s disease and their caregivers, we ask you to please consider the perspectives of patients and families as you make your important decision. For additional questions or information, please contact Sue Peschin, MHS, President and CEO of the Alliance for Aging Research, at speschin@agingresearch.org; or Chad Worz, PharmD, BCGP, Chief Executive, ASCP, cworz@ascp.com.

Sincerely,

Alliance for Aging Research
Alliance for Patient Access
Alzheimer's Los Angeles
Alzheimer’s Orange County
American Association of Post-Acute Care Nursing
American Association of Psychiatric Pharmacists
American Society for Consultant Pharmacists
Banner Alzheimer's Institute
Caregiver Action Network
CaringKind
Chambers-Grundy Center for Transformative
Neuroscience, Department of Brain Health,
UNLV
CJD Foundation
CurePSP
Dementia Alliance of North Carolina
Global Alzheimer's Platform Foundation
Global Coalition on Aging Alliance for Health
Innovation

HFC
Livpact
LuMind IDSC
Lupus and Allied Diseases Association, Inc.
Michigan State University Alzheimer's Alliance
National Certification Council for Activity
Professionals
National Consumers League
National Hispanic Medical Association
National Minority Quality Forum
Second Wind Dreams
Texas Rare Alliance
The Association of Frontotemporal
Degeneration
The Global CEO Initiative on Alzheimer's Disease
University of Rochester School of Medicine and
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