



April 3, 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. While memory loss is a well-known sign of Alzheimer’s disease (AD), agitation is nearly as prevalent, especially as the disease progresses. While 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. While cognitive impairment is regarded as the hallmark sign of Alzheimer’s disease, NPS are nearly as universal, with one or more symptoms affecting nearly all

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.

people with Alzheimer’s disease over the illness course.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 We hope that the contextual information we can contribute to the conversation will provide the committee with a fuller understanding of the nature of NPS more broadly for individuals with Alzheimer’s disease and illuminate the current substantial unmet clinical need. A May 2022 review of the AD clinical pipeline found that only 10 (6.9%) of the 143 agents identified are targeting NPS.⁴ Currently there is no Food and Drug Administration (FDA) approved medication for the on-label treatment of AAD.

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 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.⁵ 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. The signatories to this letter also appreciate the FDA Office of Neuroscience’s ongoing commitment to ensuring the safety and efficacy of treatments for people living with neurodegenerative conditions.

Substantial unmet clinical need

The development of effective therapies to prevent, delay, and better manage Alzheimer's disease is one of the most pressing and complex public health challenges facing our nation. According to the National Institute on Aging, “Alzheimer’s disease is an irreversible, progressive brain disorder that slowly destroys memory and thinking skills and, eventually, the ability to carry out the simplest tasks. It is the most common cause of dementia in older adults. While dementia is more common as people grow older, it is not a normal part of aging.”⁶ Estimates vary, but experts suggest that more

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

⁴ Cummings J, et al. *Alzheimer's disease drug development pipeline: 2022.* *Alzheimers Dement (N Y).* 2022 May 4;8(1):e12295.

⁵ 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.

⁶ <https://www.nia.nih.gov/health/alzheimers/basics>.

than 6 million Americans, most of them age 65 or older, have Alzheimer’s disease, which is currently ranked as the seventh (absent COVID-19, Alzheimer’s disease would be sixth) leading cause of death in the United States and is the only top-ten cause of death without an effective means of prevention or disease-modifying treatment. 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.

In 2015, the International Psychogeriatric Association (IPA) published a provisional consensus definition of agitation in cognitive disorders—including AAD—symptoms include at least one or more persistent behaviors that are associated with emotional distress, such as rapid changes in mood, irritability, or outbursts that cannot be attributed to another psychiatric disorder, suboptimal care conditions, medical condition, or the physiological effects of a substance.⁷ 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). Importantly, the definition notes that these behaviors are severe enough to cause significant impairment in interpersonal relationships, other aspects of social functioning, or in the person’s ability to perform or participate in daily living activities. In March 2023 the use and validation of IPA definition was summarized and the word “provisional” was removed.⁸

Off-label use of psychotropics is commonly used in AD despite the absence of a specific FDA-approved indication in this setting. It is incumbent on the clinician in these circumstances to weigh potential benefit and harm to the patient, review the consequences of not treating, and assess the appropriateness of non-pharmacological interventions prior to initiating use of a psychotropic agent. In March 2023, the IPA Agitation Workgroup responsible for the updated agitation definition 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.⁹

⁷ 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..

⁸ Sano, M., et al. (2023). *Agitation in cognitive disorders: Progress in the International Psychogeriatric Association consensus clinical and research definition*. *International Psychogeriatrics*, 1-13.

⁹ 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.¹⁰ Clinical guidelines and patient groups support first-use of non-pharmacologic and environmental interventions.^{11,12} 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.”¹³ 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. In the face of clinical need, there are regulatory and administrative challenges regarding the use of antipsychotics that have hindered clinically appropriate access.

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;¹⁴ 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.¹⁵ A 2015 study analyzed data from the Cache County Dementia Progression Study and found that psychosis, affective symptoms, agitation/aggression, mildly symptomatic neuropsychiatric symptoms, and clinically significant neuropsychiatric symptoms all were associated with earlier death.¹⁶ 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.

¹⁰ 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.

¹¹ Ibid.

¹² Alzheimer’s Association. *Challenging Behaviors*. Sept 2011. https://www.alz.org/national/documents/statements_antipsychotics.pdf

¹³ 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>.

¹⁴ 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

¹⁵ 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.

¹⁶ Tschanz JT, et al. *Progression of cognitive, functional, and neuropsychiatric symptom domains in a population cohort with Alzheimer dementia: the Cache County Dementia Progression study*. Am J Geriatr Psychiatry. 2011 Jun;19(6):532-42. doi: 10.1097/JGP.0b013e3181faec23. PMID: 21606896; PMCID: PMC3101372.

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.¹⁷ While clinical guidelines may support use for specific patient populations, the lack of on-label 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.

CMS measure on use of antipsychotics that fails to differentiate between appropriate and inappropriate use

Quality measures related to the use of antipsychotics included in the Centers for Medicare and Medicaid Services' Five-Star Rating System for Nursing Homes present additional challenges. The measures currently calculate the number of residents who received an antipsychotic divided by the total number of residents, while exempting only three conditions and providing no sensitivity to allow physicians to practice medicine or honor the wishes of residents and their families. A 2021 HHS Office of the Inspector General report found the current measure fails in its goal: distinguishing between appropriate and inappropriate use.¹⁸ Despite the identified flaws, these measures continue to factor into nursing homes' quality scores and CMS has previously considered them for inclusion in value-based purchasing (i.e., quality and reimbursement) arrangements.¹⁹ CMS's continued reliance on these incomplete measurements distorts incentives for appropriate access and care, and may lead to overdiagnosis of schizophrenia²⁰ and prescribing of other medications such as anti-epileptics that are less effective and less safe for the AAD population.

Additional considerations

While signatories to this public comment letter do not take a position on the merits of brexpiprazole for AAD, there are several additional considerations that we want to acknowledge. A primary concern with earlier generations of antipsychotics is the potential for their use as a “chemical restraint” when inappropriately prescribed. We note that many medications induce unfavorable side effects when not used according to clinical guidance and best practice. At the same time, as patient advocates, caregivers, and providers for this population, we were encouraged by the safety profile as

¹⁷ 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>

¹⁸ U.S. Department of Health and Human Services, Office of the Inspector General. *CMS Could Improve the Data It Uses to Monitor Antipsychotic Drugs in Nursing Homes*. 3 May 2021. <https://oig.hhs.gov/oei/reports/OEI-07-19-00490.asp>

¹⁹ Centers for Medicare and Medicaid Services. *Medicare Program: Prospective Payment System and Consolidated Billing for Skilled Nursing Facilities; Updates to the Quality Reporting Program and Value-Based Purchasing Program for Federal Fiscal Year 2022*. 15 Apr 2021. <https://www.govinfo.gov/content/pkg/FR-2021-04-15/pdf/2021-07556.pdf>

²⁰ Li, Xiao, et al. *Case report of first-episode psychotic symptoms in a patient with early-onset Alzheimer's disease*. BMC Psychiatry. 20:128. 17 Mar 2020. <https://bmcp psychiatry.biomedcentral.com/articles/10.1186/s12888-020-02537-9>

reported in the Phase III trial results that illustrated no statistically significant difference between the treatment and placebo arms in terms of dizziness, sedation, or deterioration of cognition.²¹ Further, we encourage the agency and Advisory Committee to consider the related evidence of safety over time in using brexpiprazole to treat schizophrenia and as an adjunctive MDD. Finally, we urge the agency to evaluate whether the class-wide black box warning for all atypical antipsychotics is still appropriate given the continued development of therapeutics in this class and more recent clinical data, or if a product-by-product evaluation of application of the warning is more appropriate.

Conclusion

We thank the FDA and the Advisory Committees for the opportunity to share our feedback and perspectives during this review. For people facing agitation associated with Alzheimer's disease and their caregivers, we support the ongoing development of safe and effective treatments to address neuropsychiatric symptoms of dementia, including agitation. 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,

Susan Peschin

Susan Peschin, MHS
President and CEO
Alliance for Aging Research



Chad Worz, PharmD, BCGP
Chief Executive
ASCP-American Society of Consultant Pharmacists

Conflict of Interest Statement: Both the Alliance for Aging Research and ASCP receive funding from a number of life science companies for non-branded health education and advocacy on age-related issues.

²¹ Agitation in Alzheimer's Dementia: Brexpiprazole phase III trial results. Presentation at Clinical Trials in Alzheimer's Disease Conference, Dec. 1, 2022.