June 3, 2022

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Re: FDA-2022-N-0557, June 17, 2022, Meeting of the Psychopharmacologic Drugs Advisory Committee

Members of the Psychopharmacologic 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 pimavanserin for Alzheimer's disease psychosis (ADP), we write to urge the Psychopharmacologic Drugs Advisory Committee 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 pimavanserin label for the treatment of hallucinations and delusions associated with ADP. While memory loss is a well-known sign of Alzheimer's disease, an estimated 30-50% of people with the disease experience psychosis sometime during their illness.[1,2] Currently there are no Food and Drug Administration (FDA) approved medications for the treatment of ADP, so this is an area of substantial unmet need.[3]

In addition to ADP, a number of emotional and mood changes, also known as neuropsychiatric symptoms (NPS), frequently occur with Alzheimer's disease and can include agitation, aggression, anxiety, sleep problems, depression, 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 people with Alzheimer's disease over the illness course.[4] The presence of NPS in people with Alzheimer's disease may worsen other clinical outcomes, leading to higher rates of cognitive and functional decline,[5] earlier time to institutionalization,

[1] Cummings J, et al. *Criteria for Psychosis in Major and Mild Neurocognitive Disorders: International Psychogeriatric Association (IPA) Consensus Clinical and Research Definition.* Am J Geriatr Psychiatry. 2020 Dec;28(12):1256-1269. doi: 10.1016/j.jagp.2020.09.002. Epub 2020 Sep 5. PMID: 32958332; PMCID: PMC7669601.
[2] Zhao QF, et al. *The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis*. J Affect Disord. 2016; 190:264–271.
[3] Ibid.
[4] 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. doi: 10.2174/1567205013666160502123607. PMID: 27137218; PMCID: PMC5070416.
[5] Stern Y, et al. *Utility of extrapyramidal signs and psychosis as predictors of cognitive and functional decline, nursing home admission, and death in Alzheimer's disease: prospective analyses from the predictors study*. Neurology. 1994;44(12):2300–2307. doi: 10.1212/WNL.44.12.2300.

and earlier death.[6] 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.

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*. Pimavanserin is an atypical antipsychotic medication that was approved by the FDA in 2016 to treat hallucinations and delusions associated with Parkinson's disease psychosis (PDP). A published 2022 systematic review and meta-analysis of the safety and efficacy of pimavanserin in the treatment of PDP found substantial reduction in hallucinations and delusions, decreased incidence of orthostatic hypotension when compared to the placebo group, and a comparable safety profile to placebo for all other adverse effects, including confusion, headaches, and falls.[7] This sNDA follows six 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 pimavanserin 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."[8] Estimates vary, but experts suggest that more 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. Only one drug has 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 amyloid-clearing medications are undergoing Phase III trials. These drugs

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

[7] Mansuri, Z., et al. *Pimavanserin in the Treatment of Parkinson's Disease Psychosis: Meta-analysis and Meta-regression of Randomized Clinical Trials.* Innovations in clinical neuroscience, 19(1-3), 46–51. 2022.

[8] https://www.nia.nih.gov/health/alzheimers/basics.

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 ADP and other neuropsychiatric symptoms.

Psychotic symptoms in Alzheimer's disease include delusions, which are fixed false beliefs that the person believes to be true, and hallucinations, which are the perception of an object or event in the absence of an external stimulus (for example, seeing, hearing, smelling, or feeling things that are not there). While delusions and hallucinations may be minor and even comforting for some individuals, more commonly they can be terribly distressing and fundamentally undermine quality of life for both the individual with Alzheimer's disease as well as their family and other care partners. Common delusions in ADP include delusions of persecution, infidelity, abandonment, or that deceased individuals (e.g., parents) are still living.[9] Other misidentification delusions also are frequent in ADP: beliefs that one's home is not one's home; that a family member is someone else, has been reduplicated, or is an imposter; the presence of phantom boarders; and that images on the television actually are people present in the house.[10] Hallucinations in ADP most commonly are visual.[11]

Psychosis occurs mostly in the mid-stages of Alzheimer's disease and may be associated with the co-occurrence of other NPS, including but not limited to agitation and aggression. Psychotic symptoms typically stop and recur intermittently but persist over time. In 2020, the International Psychogeriatrics Association (IPA) published updated criteria for psychosis in neurocognitive disorders, including Alzheimer's disease, and stated that to support a diagnosis of psychosis the symptoms should be severe enough to cause a disruption in the individuals' or others' functioning or to pose a threat to the safety of self or others (disruptions include interfering with the individual's ability to accomplish activities of daily living or interact as usual as well as limiting the ability of others to interact with them).[12]

First-generation antipsychotics have broader mechanisms of action that are relatively less specific and can cause serious side effects in older adults, namely Parkinsonism, tardive dyskinesia, and akathisia.[13] More recent studies have examined second-generation antipsychotics, such as risperidone, olanzapine, and aripiprazole for safety in older adults. These medications may be more effective for older adults with ADP, but they also have been associated with increased risk of stroke and death after short-term treatment, risks shared with

[9] Tariot PN, et al. *The Behavior Rating Scale for Dementia of the Consortium to Establish a Registry for Alzheimer's Disease*. The Behavioral Pathology Committee of the Consortium to Establish a Registry for Alzheimer's Disease. Am J Psychiatry. 1995; 152:1349–1357.
[10] Rubin EH, et al. *Nature of psychotic symptoms in senile dementia of the Alzheimer type*. J Geriatr Psychiatry Neurol. 1988; 1:17–20
[11] Ibid.
[12] Cummings J, et al. *Criteria for Psychosis in Major and Mild Neurocognitive Disorders: International Psychogeriatric Association (IPA) Consensus Clinical and Research Definition*. Am J Geriatr Psychiatry. 2020 Dec;28(12):1256-1269. doi: 10.1016/j.jagp.2020.09.002. Epub 2020 Sep 5. PMID: 32958332; PMCID: PMC7669601.
[13] Murray PS, et al. *Psychosis in Alzheimer's disease*. Biol Psychiatry. 2014 Apr 1;75(7):542-52. doi: 10.1016/j.biopsych.2013.08.020. Epub 2013 Oct 6. PMID: 24103379; PMCID: PMC4036443.

first-generation antipsychotics.[14] In contrast to antipsychotic medications, the evidence base for the efficacy of other medications, such as selective serotonin reuptake inhibitors, is much smaller.[15]

The shortcomings of antipsychotic medications to date, which were developed for similar symptoms occurring in people without dementia, may be due to a lack of biologic specificity. Older adults with neurodegenerative disorders such as Alzheimer's disease previously were excluded from trials of psychotropic medications in general, and antipsychotics specifically. Evidence from clinical, genetic, brain imaging, and neuropathology studies, now are emerging to provide an initial understanding of the neurobiology of ADP.

Barriers to meeting clinical need

The detection and assessment of ADP can be complicated, as the symptoms generally evolve over a period of months with insidious onset and slow progressive nature. Abrupt onset of psychotic symptoms suggests some other disease process such as delirium or depression. The evaluation of psychosis includes a search for medical causes such as new medications, unrecognized infections, pain, physical discomfort, urinary tract infection, constipation, delirium, polypharmacy, and environmental factors that result in overstimulation or social isolation. The expression of ADP and its management is further complicated by differences in residential setting. Many people living with moderate to severe Alzheimer's disease reside in long-term care settings, often with psychological or physical co-morbidities. Not only do these people often display different patterns of hallucinations and delusions in combination with other NPS such as agitation, aggression, or apathy, but the environment may contribute to their distress.[16]

Non-pharmacologic and pharmacologic interventions may be considered in the treatment of ADP.[17] Clinical guidelines and patient groups support first-use of non-pharmacologic and environmental interventions.[18,19] 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."[20] For patients for whom it is clinically

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[14] Ibid.
[15] Ibid.
[16] Cummings J, et al. *Criteria for Psychosis in Major and Mild Neurocognitive Disorders: International Psychogeriatric Association (IPA) Consensus Clinical and Research Definition.* Am J Geriatr Psychiatry. 2020 Dec;28(12):1256-1269. doi: 10.1016/j.jagp.2020.09.002. Epub 2020 Sep 5. PMID: 32958332; PMCID: PMC7669601.
[17] 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. https://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.2015.173501
[18] Ibid.
[19] Alzheimer's Association. *Challenging Behaviors*. Sept 2011. https://www.alz.org/national/documents/statements_antipsychotics.pdf
[20] 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:

indicated and medically appropriate given the severity or distress induced by hallucinations or delusions, access to antipsychotics can lower the incidence of symptoms and improve quality of life. Despite 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 black-box warning for second-generation antipsychotic medications about increased risk of death in elderly dementia patients;[21] 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.[22] 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.[23]

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.[24] 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 ADP. 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

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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.

[21] 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

[22] 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.

[23] 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.

[24] 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

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.[25] 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.[26] CMS's continued reliance on these incomplete measurements distorts incentives for appropriate access and care, and may lead to overdiagnosis of schizophrenia[27] and prescribing of other medications such as anti-epileptics that are less effective and less safe for the ADP population.

Additional considerations

While signatories to this public comment letter do not take a position on the merits of pimavanserin for Alzheimer's disease psychosis, there are several additional considerations that we want to acknowledge. First, we appreciate the clinical trial criteria that permitted participants between 50 and 90 years of age.[28] It is essential that clinical trials include the age-range of patients that are likely to reflect the population served by the therapeutic. However, nearly all patients in the trial were White, non-Hispanic.[29] While overrepresentation of White, non-Hispanic participants was typical of nearly all clinical studies across conditions during the study period, we are encouraged that HHS and sponsors are committed to ensuring current and future trials are representative of the intended clinical population. However, given the pervasiveness of non-representation in clinical trials overall, it would be inappropriate for reviewers to use lack of clinical trial diversity in this application as a justification for a negative decision.

As patient advocates, we also found it noteworthy that the HARMONY study was stopped early due to data demonstrating clinical benefit according to FDA-approved benchmarks in trial participants.[30] When a trial is stopped for clinical benefit, it is due to there being an ethical

[25] 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
[26] 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
[27] 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://bmcpsychiatry.biomedcentral.com/articles/10.1186/s12888-020-02537-9
[28] U.S. National Library of Medicine. *Relapse Prevention Study of Pimavanserin in Dementia-related Psychosis*. Clinicaltrials.gov. 21 June 2021. https://clinicaltrials.gov/ct2/show/NCT03325556
[29] Tariot, PN, et al. *Trial of Pimavanserin in Dementia-Related Psychosis*. New England Journal of Medicine. 22 July 2021. https://www.nejm.org/doi/full/10.1056/NEJMoa2034634
[30] Ibid.

obligation to provide the therapeutic to all trial participants (i.e. to those that previously received a placebo or a less-effective dosage) due to illustrated efficacy.[31] Though the Advisory Committee is considering a narrower label expansion (for ADP) which constituted a subpopulation of the full population in the study (all dementia-related psychosis), we believe it is instructive for the committee to evaluate the positive indicators that led to the early end of the trial. Further, we encourage the agency and Advisory Committee to consider the related evidence of safety over time in using pimavanserin to treat Parkinson's-related psychosis.

Conclusion

We thank the FDA and the Advisory Committee for the opportunity to share our feedback and perspectives during this review. For people facing Alzheimer's disease psychosis, we support the ongoing development of safe and effective treatments to address neuropsychiatric symptoms of dementia, including hallucinations and delusions. For additional questions or information, please contact Sue Peschin, President and CEO of the Alliance for Aging Research, at speschin@agingresearch.org or Ian Kremer, Executive Director of the LEAD Coalition, at ikremer@leadcoalition.org.

Sincerely,

Alliance for Aging Research
Alliance for Patient Access
Alstrom Syndrome International
Alzheimer's Los Angeles
Alzheimer's San Diego
Alzheimer's Tennessee
Alzheimer's New Jersey
Alzheimer's Orange County
American Society of Consultant Pharmacists
American Society on Aging
Association of California Caregiver Resource Centers
Banner Alzheimer's Institute
Bridge Builder Strategies
Caregiver Action Network
CaringKind, The Heart of Alzheimer's Caregiving
CJD Foundation
Cleveland Clinic Lou Ruvo Center for Brain Health, Nevada
Cognitive Dynamics Foundation

[31] Zannad, Faiez, et al. When to Stop a Clinical Trial Early for Benefit: Lessons Learned and Future Approaches. Circulation: Heart Failure. 1 Mar 2012. https://doi.org/10.1161/CIRCHEARTFAILURE.111.965707

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Michigan State University Alzheimer Alliance
National Association of Activity Professionals
National Down Syndrome Society
National Hispanic Medical Association
National Minority Quality Forum
NCCAP
Patients Rising Now
Second Wind Dreams
Society for Women's Health Research
Texas Rare Alliance
The Association for Frontotemporal Degeneration
Voices of Alzheimer’s