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February 2, 2023

Tamara Syrek Jensen, JD
Director, Coverage and Analysis Group
Center for Clinical Standards and Quality
Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

RE: Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease [CAG-00460N]

Dear Ms. Syrek Jensen,

The American Academy of Neurology (AAN) is the world's largest neurology specialty society representing more than 38,000 neurologists and clinical neuroscience professionals. The AAN is dedicated to promoting the highest quality patient-centered neurologic care. A neurologist is a physician with specialized training in diagnosing, treating, and managing disorders of the brain and nervous system. These disorders affect one in six people and include conditions such as multiple sclerosis (MS), Alzheimer's disease, Parkinson's disease, stroke, migraine, epilepsy, traumatic brain injury, ALS, and spinal muscular atrophy.

The AAN is requesting that the Centers for Medicare and Medicaid Services (CMS) begin a reconsideration process for the National Coverage Determination (NCD) published on April 7, 2022, regarding monoclonal antibodies directed against amyloid for the treatment of Alzheimer's Disease (CAG-00460N)¹. Specifically, the AAN believes that CMS should begin a focused expedited review of the NCD as it pertains to lecanemab (brand name Leqembi). CMS guidance states that a reconsideration request may be granted in circumstances in which the request includes "[a]dditional scientific evidence that was not considered during the most recent review along with a sound premise by the requester that new evidence may change the NCD decision."²

Under the current NCD, all monoclonal antibodies directed against amyloid for the treatment of Alzheimer's disease (mAbs) are subject to Coverage with Evidence Development (CED) requirements upon being granted

¹National Coverage Determination (NCD) for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (CAG-00460N), Centers for Medicare & Medicaid Services (Apr. 7, 2022), <https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=305> (Apr. 2022 Alzheimer's Decision Memo).

² 78 Fed. Reg. At 48167

approval by the Food and Drug Administration (FDA)³. The NCD specifies that therapies in this class that are approved based on evidence of efficacy from a change in a surrogate endpoint, as is consistent with the Accelerated Approval Pathway,⁴ are only covered in the context of randomized controlled trials. Therapies approved based on evidence of efficacy from a direct measure of clinical benefit may be covered in CMS approved or NIH supported prospective comparative studies.⁵⁶ In this NCD, and in guidance issued by CMS on the CED requirements, CMS stated that as further evidence becomes available that supports consideration of a change in the coverage status of the item or service, a revised NCD could be expedited.⁷⁸

In explaining the purpose of the NCD requirements, CMS noted that “(t)o date, no large, pivotal RCT, or set of RCTs, of an antiamyloid mAb has been completed, with a trial report published in the peer-reviewed medical literature demonstrating a clear (non-conflicting) improved health outcome (i.e., a meaningful clinical benefit in terms of slowing in the decline of cognition and function) for Medicare beneficiaries with AD.”⁹ CMS further noted that “clear evidence about the clinical benefits and harms of any drug in this antiamyloid mAb class is needed for Medicare beneficiaries with early AD to make, along with their physicians and trusted advisors, informed decisions about whether the treatment is appropriate for them.”¹⁰

Although the AAN has not taken a position on whether lecanemab ought to receive traditional FDA approval, there is consensus among the AAN’s member experts and leadership who have reviewed the phase III data that the CLARITY AD trial was well-designed, and its findings are clinically and statistically significant. The AAN concurs with CMS that at the time of the NCD’s release, critical questions remained regarding the efficacy of mAb products for the treatment of Alzheimer’s Disease. These critical questions were summarized in three specific questions to be addressed through CED. The AAN’s answers to those questions and the AAN’s interpretation of recently released data are as follows:

- a. Does the antiamyloid mAb meaningfully improve health outcomes (i.e., slow the decline of cognition and function) for patients in broad community practice?

The phase III data from the CLARITY AD trial was published in the *New England Journal of Medicine (NEJM)* on January 5, 2023.¹¹ The AAN concurs with the authors of the paper, entitled “Lecanemab in Early Alzheimer’s Disease” that treatment with lecanemab, “resulted in moderately less decline on measures of

³ Section I.A. Apr. 2022 Alzheimer’s Decision Memo

⁴ Section I.B.1 Apr. 2022 Alzheimer’s Decision Memo

⁵ Section I.B.2 Apr. 2022 Alzheimer’s Decision Memo

⁶ Sections I.B.3-5 Apr. 2022 Alzheimer’s Decision Memo

⁷ Apr. 2022 Alzheimer’s Decision Memo

⁸ Guidance for the Public, Industry, and CMS Staff: Coverage with Evidence Development, Centers for Medicare & Medicaid Services (Nov. 20, 2014) <https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?MCDId=27>

⁹ Apr. 2022 Alzheimer’s Decision Memo

¹⁰ Apr. 2022 Alzheimer’s Decision Memo

¹¹ Christopher H. van Dyck et al., Lecanemab in Early Alzheimer’s Disease, *NEW ENGLAND J. MED.* (Nov. 29, 2022)

(“Van Dyck et al.”)

cognition and function than placebo.” The AAN notes that Alzheimer's disease and associated dementia can lead to many challenges for patients and caregivers. Therefore, meaningful improvement may take many forms. Stabilization, improvement, or meaningful slowing of decline in cognitive function and independent functioning, both in the community and at home, are the most meaningful outcomes for patients receiving these treatments. The AAN believes the findings of the phase III trial are indicative of meaningful improvement. Data presented showed therapeutic benefit on not just surrogate endpoints, such as amyloid clearance, but also cognitive endpoints including the slowing of cognitive dysfunction and a decrease in the decline of activities of daily living. The AAN believes these findings support the need for broader access to lecanemab than currently permitted under the NCD.

- b. Do benefits, and harms such as brain hemorrhage and edema, associated with use of the anti-amyloid mAb, depend on characteristics of patients, treating clinicians, and settings?

The AAN believes that, upon further study, patient factors such as disease stage and preexisting level of function will be associated with benefits of treatment and that patient populations that are reflective of the trial populations are likely to derive the same amount of mean benefit. The AAN also believes that certain patient factors are likely to lead to distinct side effect profiles. Preexisting microbleeds, use of anti-coagulants, and the presence of at least one ApoE4 gene variant may indicate higher risk for ARIA-related complications. The AAN is eager for additional study on this class of therapies, and lecanemab specifically, but believes that existing information provides a framework to reasonably stratify benefits and risk.

In relation to how benefits and harms depend on the treating clinician and setting, the AAN believes that facilities should be appropriately licensed, with trained personnel to administer the medication and monitor patients during infusions. Care should be overseen by trained physicians with experience in treating Alzheimer's disease patients and the expertise needed to monitor for the adverse events associated with this medication, including ARIA E and ARIA H. It is also critical to promote communication between the treating clinician and the infusion center to ensure appropriate adjustments are made to the plan of care should ARIA or other contraindications arise or worsen.

- c. How do the benefits and harms change over time?

The AAN shares CMS' commitment to ensuring patients are receiving the most appropriate and effective treatments possible and that those considerations incorporate the harms and benefits of FDA-approved products over time. However, the AAN believes that this question is not reasonably able to be answered given the existing body of published evidence. The AAN does believe that, while the data indicates that incidence of isolated ARIA H does not decrease with time, the incidence of mixed ARIA is more common in the first six months of treatment.

Although this question cannot be fully elucidated at this time and warrants further study, the AAN does not believe absence of longitudinal data should be sufficient reason for the agency to restrict access to a treatment for patients in dire need, with no other FDA-approved treatment options to meaningfully impact disease progression. There is clear unmet need for the Alzheimer's disease population and the AAN does not believe that it is appropriate to substantially limit patients' access to therapy solely based on this criterion.

Alternatively, CMS could explore how best to work with both the FDA and the manufacturer to ensure that appropriate post-market surveillance occurs and to ensure that the NCD is updated in a timely manner if persuasive evidence emerges indicating either increased risk of adverse events or diminished benefit over time. The AAN believes that real world use of the drug can be a helpful longitudinal tool to further establish how benefits and harms change over time. The AAN will be eager to continue to collaborate with regulators to ensure that patients are receiving optimal care as this data is reported.

Throughout the National Coverage Analysis (NCA) and NCD processes, the AAN repeatedly raised concerns regarding the potential unintended consequences of applying this NCD to the entire class of mAbs for the treatment of Alzheimer's disease. The AAN is concerned that absent a reconsideration of the NCD, patients who could benefit from lecanemab will be denied access, due to restrictions found in the NCD, leading to irreversible disease progression that could have been slowed with treatment. At the time of the release of the NCD, aducanumab (brand name Aduhelm) was the only approved therapy of its kind that would be subject to the NCD, and the available data did not persuasively demonstrate meaningful clinical benefit for patients affected by Alzheimer's disease. Given these facts, the AAN believed that the NCD was broadly appropriate at the time. However, as of January 6, 2023, lecanemab has been granted accelerated approval by the FDA.¹² Although traditional approval is pending and the FDA has not yet considered the phase III data, as noted above, the AAN believes that data from the phase III CLARITY AD trial provides persuasive evidence that indicates meaningful direct clinical benefit, which upon traditional approval would warrant reconsideration of the NCD.

Although the AAN is supportive of modifying the NCD, we would also like to note the substantial impact that broadened coverage of lecanemab is expected to have on the health care system at large. Given the sizable patient population for whom lecanemab may be prescribed, the AAN does believe that pressure will mount on providers and patients alike. There will be a need for additional resources for neurologists and their support staff to accommodate the substantial increase in infusion and monitoring services for these patients and the AAN has already begun identifying and developing resources for our members and their patients to this end. Additionally, the AAN notes that our members have expressed concerns relating to the costs associated with this medication and the impact that this will have both on patient access and on the broader healthcare system. Neurologists seek to provide high-value care for patients with neurological disease at the lowest cost possible and

¹² FDA Grants Accelerated Approval for Alzheimer's Disease Treatment, U.S. Food and Drug Administration (Jan. 6, 2023) <https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-disease-treatment>

we welcome the opportunity to serve as a resource to promote access to high-value medications.

To summarize, the AAN believes that the phase III data from the CLARITY AD trial indicating a direct clinical benefit warrants a focused expedited reconsideration of the existing coverage policy as it applies to lecanemab, as it would have been impossible for CMS to consider this highly relevant data at the time that the NCD was published. We believe to promote patient access to therapy, that it would be appropriate for this reconsideration to occur so that a revised decision can be released with an effective date concurrent with a potential traditional approval of lecanemab. Furthermore, the AAN believes that a similar approach could be applied to future products which meet the standard set by the phase III data published in NEJM.

The AAN appreciates the opportunity to engage on this issue and for the continued dialogue between CMS and the AAN. The AAN was heavily involved in the NCA that preceded this NCD and submitted official comments¹³ on the proposed decision memo with the intent to aid CMS in establishing prudent coverage policy for this class of therapies. The AAN wishes to reiterate our gratitude to CMS for its diligent response and attention to the need to ensure that Medicare beneficiaries have access to safe and effective treatments. We understand and appreciate that the time and effort required to reach a NCD is substantial. Our members care for the millions of Alzheimer's patients enrolled in Medicare and are grateful for the thoughtful consideration of these issues. The AAN's member experts are eager to continue lending expertise to CMS. If you have any questions regarding these comments or seek further input, please contact Matt Kerschner, Director, Regulatory Affairs at mkerschner@aan.com or Max Linder, Government Relations Manager at mlinder@aan.com.

Sincerely,

A handwritten signature in black ink that reads "Orly Avitzur MD". The signature is written in a cursive, flowing style.

Orly Avitzur, MD, MBA, FAAN
President, American Academy of Neurology

¹³ American Academy of Neurology Proposed National Coverage Determination Comment Letter (Feb. 4 2022) <https://www.aan.com/siteassets/home-page/tools-and-resources/practicing-neurologist-administrators/aducanumab/2022.02.04-final-aan-amyloid-ncd-comments.pdf?epiprojects=13>