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June 12, 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: Formal Reconsideration Request: 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 40,000 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 submitting an amended request that the Centers for Medicare and Medicaid Services (CMS) formally reconsider 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 reconsider the NCD as it pertains to lecanemab (brand name Leqembi). This letter updates our request submitted on February 2, 2023, based on an ongoing collaborative effort between the AAN and CMS to determine the most appropriate coverage policy for this therapy. This letter contains our full recommendations and refines our request based on the AAN's understanding, through virtual meetings and email communications with CMS, of CMS' commitment to moving forward with Coverage with Evidence Development (CED) requirements for lecanemab and our mutual interest in ensuring that patients receive coverage under the least restrictive

[1]National 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).

policy feasible. This reconsideration request is based on the AAN's assessment of recently published evidence as well as the clear unmet need for Alzheimer's patients to have access to appropriate therapies. 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]

Background

Under the current NCD, all monoclonal antibodies directed against amyloid for the treatment of Alzheimer's disease (mAbs) are subject to CED requirements upon being granted 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.[5][6] 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.[7][8]

In explaining the purpose of the CED 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 anti-amyloid 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]

The AAN is formally requesting that this NCD be reconsidered and amended should lecanemab be granted traditional approval by the FDA to ensure broader and more equitable access for appropriate patients. 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 recognizes the existence of gaps in the available body of literature and that CMS seeks to answer three key

[2] 78 Fed. Reg. At 48167
[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

questions using the CED requirements laid out within the NCD, but the AAN does not believe CED is appropriate for all patients who may receive this treatment.

Proposed Coverage with Criteria Framework

AAN subject matter experts have reviewed the CED requirements under the current NCD and currently available data, including the data published in the *New England Journal of Medicine* (NEJM), and determined that upon traditional approval, patients matching the below criteria should be able to receive lecanemab without being required to participate in registry-supported prospective comparative studies. The AAN believes it is appropriate that patients not meeting the below criteria but who are likely to receive benefit from treatment receive lecanemab in the context of a prospective comparative study. However, the AAN firmly believes that CED should not be a long-term solution and that the goal of this coverage policy should be to identify the most appropriate patients for this class of therapies and expeditiously transition them from being subjected to CED requirements to receiving broad, equitable, and unfettered coverage as long as they meet evidence-based criteria. Furthermore, the AAN believes it is critical for CED to have a predetermined timeline for interim data analysis, and if that analysis demonstrates that the study endpoints have been met, that the CED should be stopped and full coverage be established.

The AAN is proposing a two-pronged coverage schema under which a subset of Medicare beneficiaries would have access to lecanemab without being subject to CED (which we refer to as the "coverage with criteria" population) and a second population of patients would be subject to CED requirements. The AAN believes that patients should be covered under CED if they meet any of the below exclusion criteria and their provider reasonably believes that the patient is likely to derive meaningful clinical benefit. The AAN's proposed coverage framework is described below:

Proposed Coverage with Criteria: Patient Characteristics:

- Diagnosis: Mild Cognitive Impairment (MCI) due to Alzheimer's disease–- intermediate likelihood:
    - Meet the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria for MCI due to Alzheimer's disease – intermediate likelihood
    - Report a history of subjective memory decline with gradual onset and slow progression over the last 1 year before treatment initiation; must be corroborated by an informant, or
- Diagnosis: Mild Alzheimer's disease dementia:
    - Meet the NIA-AA core clinical criteria for probable Alzheimer's disease dementia

Proposed Coverage with Criteria: Inclusion Requirements (all of the following must be met):

- Objective impairment in memory or thinking corroborated on bedside (e.g., MMSE, MoCA) or formal neuropsychological testing with minimal impairment in day-to-day function
- Positive biomarker for brain amyloid pathology via CSF or PET

- Male or female participants aged greater than or equal to (>=) 50 and less than or equal to (<=) 90 years, at the time of informed consent
- Mini mental state examination (MMSE) score >=22 at treatment initiation and baseline
- Body mass index (BMI) greater than (>)17 and less than (<) 35 at treatment initiation
- Have an identified care partner (defined as a person able to support the participant for the duration of the therapy)

Proposed Coverage with Criteria: Exclusion Conditions:

- Any neurological condition that may be contributing to cognitive impairment above and beyond that caused by the participant's Alzheimer's disease
- History of transient ischemic attacks (TIA), stroke, or seizures within 12 months of treatment initiation
- Any psychiatric diagnosis or symptoms (example, hallucinations, major depression, or delusions) that could interfere with the patient's ability to adhere to the monitoring regimen
- Contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (example in skull and cardiac devices other than those approved as safe for use in MRI scanners)
- Evidence of other clinically significant lesions on brain MRI at treatment initiation that could indicate a dementia diagnosis other than Alzheimer's disease
- Other significant pathological findings on brain MRI at treatment initiation, including but not limited to: more than 4 microhemorrhages (defined as 10 millimeter [mm] or less at the greatest diameter); a single macrohemorrhage > 10 mm at greatest diameter; an area of superficial siderosis; evidence of vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease; space occupying lesions or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts that are <1 centimeter [cm] at their greatest diameter need not be exclusionary)
- Any immunological disease which is not adequately controlled, or which requires treatment with immunoglobulins, systemic monoclonal antibodies (or derivatives of monoclonal antibodies), systemic immunosuppressants, or plasmapheresis during treatment
- APoe4 Homozygote positivity
- Participants with a bleeding disorder that is not under adequate control (including a platelet count < 50,000 or international normalized ratio [INR] > 1.5 for participants who are not on anticoagulant treatment, example, warfarin)
- Patients who are on anticoagulant therapy
- Any other medical conditions (example, cardiac, respiratory, gastrointestinal, renal disease) which are not stable and adequately controlled, or which in the opinion of the provider could affect the patient's safety
- Patients with autosomal dominant AD, including trisomy 21

Although we are not recommending that they be excluded, careful consideration should be made by the provider for patients with prior exposure to anti-amyloid mAb therapy.

AAN Response to CED Questions

Currently, Medicare coverage for lecanemab is limited by CED. The AAN makes this reconsideration request with the goal of mitigating any undue restrictions on access resulting from the CED policy. The AAN believes it is of the utmost importance to critically evaluate the current body of evidence as it pertains to the CED questions. It is the AAN's belief that the three CED questions laid out within the NCD have been sufficiently answered for the proposed "coverage with criteria" patient population, and we therefore believe that these patients should not have their access to this therapy limited by the constraints of CED. Our reasoning for each of these questions, as stated in our letter dated February 2, 2023, with minor clarification, 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 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 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 does not believe there is adequate reason to doubt the applicability of these results to the proposed "coverage with criteria" population, as that population very closely mirrors the patient population of the CLARITY AD trial. 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 this question has been satisfactorily answered, by existing data for lecanemab, for the patient population included in our proposal for "coverage with criteria." The AAN believes that these patients would receive a similar amount of mean benefit from treatment as the trial population, with similar safety profiles, and therefore should be removed from CED. However, the AAN believes that, upon further study, for patients outside of the "coverage with criteria" population (e.g.,

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

those with an excluded condition), patient factors such as disease stage and preexisting level of function may be associated with varied benefits of treatment. 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. This distinction among patient populations is the basis for our request to remove the proposed patients from the CED requirement, as we believe that the safety and efficacy questions for these patients have been addressed.

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. Regardless of the mechanism for coverage, 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 believes this question has been satisfactorily answered, by existing data on lecanemab, for the patient population we propose for "coverage with criteria." The AAN also notes that this is an open-ended question and could be interpreted to mean that 10 or more years of follow-up is needed for a final answer. The AAN believes any CMS-approved CED trial must include an agreed-upon length of follow-up at which time an interim analysis can be performed to determine if this question is satisfactorily answered for the CED population or a subset thereof.

The AAN shares CMS' commitment to ensuring patients receive the most appropriate and effective treatments possible and that those considerations incorporate the harms and benefits of FDA-approved products over time. The AAN acknowledges that this question is not reasonably able to be answered for the proposed CED population 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 for the CED population, 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 our proposed "coverage with criteria" population, as there are 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.

The AAN is eager to continue to work with the FDA, CMS, and other stakeholders to monitor developments in the published evidence as this therapy is administered. This includes the AAN's continued collaboration in exploring how best to develop and operationalize the registry-supported prospective comparative studies required for coverage of this therapy for patients outside of the proposed "coverage with criteria" population. Furthermore, 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.

Rationale for Reconsideration Request

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 that 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 fully 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 for appropriate patients. The AAN believes that CMS should take this opportunity to implement the "off-ramp" to full coverage recommended by the AAN in our comments[13] in order to facilitate adjustments to this NCD as quickly as possible, as evidence is gathered.

This reconsideration is critically necessary in order to mitigate the substantial limitations on access to this therapy inherent in the existing CED design. The AAN understands the importance of thorough and accurate evidence gathering to address gaps in existing data on the safety and efficacy of this therapy for certain patient populations and thus the need for CED requirements for those patients. However, requiring participation in a registry-supported prospective comparative study for patients who meet our "coverage with criteria" population will represent a substantial barrier for providers and patients alike. The AAN

[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

[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

acknowledges the initiative announced recently to develop a "nationwide CMS-facilitated portal" in order to address the existing gap in technical infrastructure to support the existing coverage policy.[14] However, the AAN believes that the announced web-portal is unlikely to address many of the underlying issues inherent to requiring registry participation as a condition of coverage for all patients. The AAN has significant concerns related to the burdensome nature of the CED requirements for institutions that would seek to participate and anticipates that complying with a registry-supported study will likely be a lengthy and complex process. Data collection and reporting requirements are likely to dampen participation and may be exclusionary for smaller community practices for whom study participation may be infeasible. Furthermore, it is the understanding of the AAN that, at present, no such study has been approved by CMS that could leverage a registry to fulfill CMS' commitment to "broader coverage using the framework we announced last year, under coverage with evidence development, on the same day [as traditional approval]."[15] The AAN is committed to addressing these operational concerns to the best of our ability but notes that there are significant and time-consuming challenges that will assuredly need to be addressed before any registry supported study can effectively implement the CED requirements. For all the reasons described in this letter, the AAN believes that CMS should adopt our recommendation for "coverage with criteria" so patients for whom the benefit and safety profile has been well established are eligible for lecanemab in the normal course of care.

Conclusion

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 treatment challenges will mount for 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 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. While the AAN believes that registry-supported prospective comparative studies may be an appropriate context for coverage for certain patients, the patients described above in the "coverage with

[14] CMS announces plan to ensure availability of new Alzheimer's drugs (Jun. 1. 2023) https://www.cms.gov/newsroom/press-releases/cms-announces-plan-ensure-availability-new-alzheimers-drugs
[15] CMS Statement on FDA Accelerated Approval of Lecanemab (Jan. 6 2023) https://www.cms.gov/newsroom/press-releases/cms-statement-fda-accelerated-approval-lecanemab

criteria" framework should not be limited in their access given the existing evidence demonstrating lecanemab's safety and efficacy.

The AAN strongly encourages and is committed to working with CMS and all stakeholders to ensure, if our framework is accepted, that evidence is expeditiously evaluated, and patients are able to transition from being subject to CED to receiving coverage with criteria as appropriate. Furthermore, the AAN believes that a similar approach could be applied to future products which meet or exceed the evidentiary standard set by the phase III data published in NEJM. The AAN believes that CMS should proactively consider how the AAN's proposed framework could be applied expeditiously and appropriately to additional forthcoming products that may seek FDA approval.

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 comments[16] 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 membership is 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 and Policy at mkerschner@aan.com or Max Linder, Government Relations Manager at mlinder@aan.com.

Sincerely,

Carlayne E. Jackson, MD, FAAN
President, American Academy of Neurology

[16] 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