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February 4, 2022

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 (AD), Parkinson's disease, stroke, migraine, epilepsy, traumatic brain injury, ALS, and spinal muscular atrophy.

The AAN is grateful to the Centers for Medicare and Medicaid Services (CMS) for its diligent response to aducanumab's approval and the agency's attention to the need to ensure that Medicare beneficiaries have access to safe and effective treatments. We understand and appreciate the decision to launch a National Coverage Analysis (NCA) in response to the approval of aducanumab and note that the time and effort required to reach a National Coverage Determination (NCD) is substantial. The AAN appreciates the opportunity to comment on this NCD and notes that we have been engaged with regulators and stakeholders throughout the aducanumab approval and coverage determination process. The AAN's primary objective in responding to this request for comment is to ensure that patients suffering from AD have access to the best possible care and that the search for curative therapies is supported.

Application of NCD to the Entire Class

The AAN notes that we have provided comment to the Food and Drug Administration (FDA)[1] prior to the approval of aducanumab and to

[1] AAN Comments to FDA Advisory Committee on Aducanumab Labeling | October 22, 2020

CMS during the NCA[2] requesting that proof of amyloid biomarker abnormalities should be required for treatment and that treatment should be limited to patients with a diagnosis of mild Alzheimer's disease or mild cognitive impairment (MCI) due to AD (Mini-Mental Status Exam between 24-30 and Clinical Dementia Rating of 0.5). The AAN has also worked to expand access to amyloid positron emission tomography (PET) imaging to confirm amyloid positivity to help identify patients for whom these therapies may be effective. This NCD realizes many of the AAN's priorities. These include coverage of PET to confirm amyloid positivity for prospective patients, limitation of coverage to patients with mild cognitive impairment or mild AD, further clinical trials to confirm clinical benefit, and more inclusive trial data to reflect the diverse patient population affected by AD.

However, the AAN is concerned that this NCD is being applied to the entire class of monoclonal antibodies (mAbs) directed against amyloid for the treatment of AD. While aducanumab is currently the only approved therapy of its kind, there are multiple therapies in various stages of the approval process that work through the same mechanism but for which the full body of evidence is not currently publicly available. The AAN is concerned that results from trials in progress for upcoming therapies may demonstrate evidence of meaningful clinical benefits that will not warrant the same restrictions as proposed in this NCD.

The AAN believes that the Coverage with Evidence Development (CED) included in this determination is prudently designed to investigate the safety and effectiveness of these therapies. However, should further study of aducanumab, or any other mAb, yield clinically meaningful results in the treatment of AD, a mechanism must be in place to remove that therapy from the constraints of this NCD and allow widespread access as quickly as possible. **As such, the AAN requests that an "off-ramp" be created within this NCD that would allow for a therapy demonstrating safety and effectiveness to be reconsidered without the need to restart the NCA/NCD process.** Criteria should be developed to determine which therapies no longer need to be constrained by the CED. The AAN believes that criteria may include clinically meaningful differences in decline on the Clinical Dementia Rating Sum of Boxes (CDR-SB), decreased decline on a cognitive screen, and improvement on a functional screen. The AAN notes that CMS should not view the above criteria as a comprehensive list, but rather as being representative of the types of tools CMS should consider when evaluating the performance of these therapies and welcomes the opportunity to engage with the agency regarding the appropriateness of criteria.

Should the FDA approve a new amyloid therapy that is proven to be safe and clinically effective, the AAN is deeply concerned that patients may be denied access while waiting for this NCD to be altered or otherwise be limited to accessing the newly approved product through a trial under the proposed CED. Since the approval of aducanumab in June 2021, the AAN believes that providers have demonstrated their ability to make decisions jointly with their patients on whether a new drug is appropriate for each given circumstance. Should each new amyloid therapy start from a position of extremely limited coverage, regardless of demonstrated benefit, patients without the means to access care under the NCD will effectively be barred from accessing treatment. **The AAN requests that this NCD be**

[2] AAN provides comments to CMS on coverage for aducanumab | August 9, 2021

limited to only aducanumab while establishing a process to allow new therapies in this class to be individually judged on their safety and effectiveness.

Coverage with Evidence Development (CED)

The AAN notes that we have voiced concerns over the process that resulted in the approval of aducanumab. We are grateful to CMS for the thought and intention behind requiring CED for its use. This tool will allow CMS to gather additional data on aducanumab that will be integral in informing care decisions in the future. The following are suggestions that the AAN has regarding the implementation of CED to maximize its investigative reach while minimizing disruption to patients and providers.

Hospital-Based Outpatient Setting:

One of the AAN's most pressing concerns with the proposed NCD is the requirement that provision of these therapies be restricted to "hospital-based outpatient settings." While the AAN agrees that close monitoring and access to an adequately trained care team are critical, the "hospital-based outpatient setting" is not the only setting where this therapy can be safely administered. The AAN believes that the proposed requirement would restrict access to care in many clinical practices. A significant portion of trialists in aducanumab's phase three trials, as well as ongoing trials for other mAbs, do not work in this strictly defined setting. Many operate in infusion centers, private practices with robust clinical research centers, or within a large medical center, but not necessarily on a floor or unit that is categorically defined as a hospital outpatient department. **It is critical for patient access and trial integrity that the "hospital-based outpatient setting" requirement be revised to include infusion centers and other settings not strictly designated as a hospital outpatient department.** The AAN believes that rather than implementing this limitation, the agency should focus on ensuring that services are provided by clinicians and staff with expertise in the treatment of AD and promoting communication between the treating clinician and the infusion center to ensure that patients do not receive the mAb when they have amyloid-related imaging abnormalities (ARIA) or another contraindication.

The AAN believes that the first year of treatment is the highest risk for the development of ARIA, so infusions should be provided in an infusion center during this period. After the first year of infusions, we would support flexibility to allow for provision within a home infusion setting, as eligible patients may have transportation challenges and could benefit from the ability to receive home infusion therapy. While a patient is receiving care at home, they should continue to receive care and be monitored by a care team member who has received training in monitoring and caring for patients receiving this class of drug. Care should be given by a physician who can identify appropriate patient populations to receive this medication. This includes coordination of screening studies, including baseline magnetic resonance imaging (MRI), detection of beta-amyloid, and appropriate cognitive evaluations. Appropriate care also includes coordinating ongoing management of the patient as they receive therapy, monitoring for clinical and radiographic signs of ARIA, and general monitoring of the patient's health and wellbeing.

Research Questions:

The AAN fully supports the proposed research questions in this NCD. These questions are well designed to fill gaps in existing data to help patients and providers make appropriate treatment decisions.

Validated Cognitive and Functional Instruments in CED Trials:

The following are examples of instruments that the AAN believes are effective in the measurement of cognitive and functional decline in patients with AD. This list is not necessarily comprehensive but is intended to demonstrate potential considerations for CMS when evaluating instruments:

- Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog)
- Alzheimer's Disease Cooperative Study Activities of Daily Living Scale (ADCS-ADL)
- Alzheimer's Disease Cooperative Study Instrumental Activities of Daily Living (ADCS-iADL)
- Zarit Burden Interview (ZBI)
- Mini-Mental Status Exam (MMSE)
- Montreal Cognitive Assessment (MoCA)
- Katz Index of Independence in Activities of Daily Living (ADL)
- Lawton Instrumental Activities of Daily Living Scale (IADL)
- Functional Activities Questionnaire (FAQ)
- Neuropsychiatric Inventory (NPI)
- Global Clinical Dementia Rating (Global CDR)
- Clinical Dementia Rating Sum of Boxes (CDR-SB)

Clinically Meaningful Improvement:

Alzheimer's disease and associated dementia can lead to many challenges for patients and caregivers. Therefore, meaningful improvement may take many forms. It is also notable that aducanumab, and likely other mAbs that are yet to be approved, do not purport to reverse cognitive decline but instead slow its progression. 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. These outcomes can be measured by using standardized dementia scales and other functional measures. Examples of dementia scales the AAN would recommend include MMSE, MOCA, CDR-SB, Katz ADL, and Lawton IADL. Due to varying rates of decline among the patient population, even using objective scales, it might be difficult for a patient being treated to tell if their decline is occurring less quickly on therapy. Therefore, insight from the treating physician is necessary. **It is critical that CMS not be overly restrictive in its trial approval criteria as trialists may aim to study a variety of qualitative and quantitative measurements for determining meaningful benefit.**

<u>Patient Criteria:</u>

Inclusion Criteria

The AAN is grateful to CMS for their recommendations, consistent with our advocacy, to limit coverage to patients with proven amyloid positivity and those suffering from MCI due to AD or mild AD dementia.

We appreciate the decision by CMS to allow for coverage of an amyloid PET scan to confirm amyloid positivity. However, limiting coverage to one scan per patient may have the unintended consequence of reducing access for patients who may develop amyloid positivity later in their disease progression. There may also be other circumstances in which the clinician believes an additional scan is warranted. Such circumstances include but are not limited to technical issues with tracer, movement artifact, development of new cognitive symptoms, or the initial scan being done when the patient is not symptomatic. Therefore, the AAN believes that the agency should account for these circumstances and allow clinicians covered by the CED to exercise their professional judgment to request coverage in cases in which an additional scan may be necessary.

Exclusion Criteria:

The AAN recommends that patients should be excluded if their baseline MRI shows four or more microhemorrhages or evidence of superficial siderosis. However, the AAN advises caution in the broadness of exclusion criteria that may prevent trialists from responsibly studying the effect of these new therapies on patients with certain comorbidities. As an illustrative example, 30 percent of patients with AD have concurrent vascular dementia. Patients with anything more than minimal vascular changes on the initial MRI have been excluded from relevant clinical trials in the past. The AAN believes that the frequency of this concurrence may warrant the inclusion of patients with vascular burden in the trial population. The AAN believes that it is prudent to make decisions on the exclusion of these patient populations at the individual trial level with specific consideration of contraindications that may signify a higher risk of ARIA-H or other harmful side-effects.

<u>Health Disparities:</u>

The AAN has fervently advocated for improving the representation of diverse populations in clinical trials. We agree wholeheartedly with CMS' description of the inequity inherent in the research and treatment of AD in Black and Hispanic patient populations. **As such, the AAN recommends that each trial be required to demonstrate the methodology for recruiting and retaining diverse participant populations, as supported by health care institutions around the world and in the USA in alignment with National Institutes of Health standards, including Guiding Principles for Ethical Research[3] and Ethics in Clinical Research.[4] In support of this effort, CMS should work to address disparities based on geography, race, and other socio-economic factors by providing resources to address barriers to trial participation for historically underrepresented populations.**

One such barrier is the potentially prohibitive cost-sharing a patient may be responsible for voluntarily agreeing to participate in these trials that have inherent risks to the

[3] Guiding Principles for Ethical Research | March 16, 2016
[4] Patient Recruitment: Ethics in Clinical Research | October 21, 2021

participant. Furthermore, the AAN has concerns that the likelihood of high out-of-pocket costs will skew access to these trials and, by extension, these therapies towards an unrepresentative patient population. Additionally, the AAN believes that CMS must account for the challenges associated with a double-blind, randomized control trial if patients are responsible for different cost-sharing amounts depending on their receipt of the therapy or the placebo. **Finally, CMS should structure coverage of trial costs to limit financial barriers to participation for patients with limited financial resources due to the impacts that they may have on participant representativeness.**

The AAN appreciates the opportunity to comment on this proposed NCD and the continued dialogue between CMS and the AAN. Our members care for the millions of Alzheimer's patients enrolled in Medicare and are grateful for the thoughtful consideration of these issues. AAN member experts are eager to continue lending expertise to CMS as this NCD is finalized. 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,

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