

August 11, 2021

Chiquita Brooks-LaSure
Administrator
Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

Re: National Coverage Analysis (NCA) Tracking Sheet for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease

Dear Administrator Brooks-LaSure:

The American Geriatrics Society (AGS) appreciates the opportunity to comment on the Centers for Medicare and Medicaid Services (CMS) National Coverage Analysis (NCA) Tracking Sheet for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease. Our nearly 6,000 members are geriatricians, geriatric nurses, nurse practitioners, social workers, family physicians, physician assistants, pharmacists, internists, and specialty physicians who are dedicated to improving the health, independence, and quality of life of older adults.

We believe that the evidence is insufficient for CMS to issue a National Coverage Determination (NCD) for the entire class of monoclonal antibodies directed against beta amyloid for the treatment of Alzheimer's disease (AD). In light of that, we ask that CMS carefully consider whether such a step is justified, given that only one such monoclonal antibody, aducanumab, is U.S. Food and Drug Administration (FDA) approved. Further, there is substantial evidence of heterogeneity across the various antibodies and trial designs that have been, are being, and will be tested. Specifically, the Phase 3 trials currently in process that are intended to support FDA approval of other monoclonal antibodies in this class have different trial designs than the aducanumab trials, and will likely have different FDA-approved indications, safety profiles, patient benefits, and requirements for administration. Therefore, we think it is premature to make a coverage determination for any product other than aducanumab.

We also caution that establishing coverage criteria based on FDA-approved indications may not be sufficient given that the FDA-approved indications and diagnostic requirements for prescribing aducanumab differ significantly from what was studied in trials (see Observations below). For these reasons, we believe that CMS must require evidence collection as a part of its coverage determination given the insufficient data available to demonstrate safety and effectiveness. **It is critically important that an NCD for aducanumab issued by CMS ensure that any patient who has non-Alzheimer's dementia or later stage AD, is not prescribed aducanumab.** At this juncture, the FDA-approved label lacks the guardrails that are needed to ensure that Medicare beneficiaries who do not have beta amyloid positivity or have later stage AD or another type of dementia are not prescribed aducanumab.

In preparing this comment, we have carefully reviewed the FDA-approved label for aducanumab, the discussion at the FDA advisory committee, the Institute for Clinical and Economic Review's (ICER)

comments on aducanumab, and the publicly available information about the FDA analysis of the aducanumab clinical trials.

OBSERVATIONS AND RECOMMENDATIONS

As a preliminary matter, we note that it is very likely that the patients who will receive aducanumab in clinical practice will be significantly different than the patients who were studied in the ENGAGE and EMERGE clinical trials. With that in mind, and based on our review, we offer the following observations and recommendations to CMS.

Observations

1. The FDA approval, under its fast-track pathway, was based on a surrogate outcome – the reduction of beta amyloid plaque in the brain – and the belief that such reduction may be associated with improved cognitive function. No improvement in cognitive function was demonstrated in the clinical trials. Aducanumab may slow cognitive decline in some patients with AD but this was not demonstrated in the clinical trials which were halted after a futility analysis by an independent review panel determined that it was unlikely to outperform the placebo.
2. The patient population studied in the two Phase 3 clinical trials for aducanumab, ENGAGE and EMERGE, was very limited. There were very few participants from underrepresented, disproportionality affected, or understudied populations in the trials. It is unclear if the evidence from the trials can be generalized to these populations. In addition, patients on anticoagulation or with other cerebral pathology (e.g., previous stroke) were excluded. This means that there is no evidence that aducanumab will be safe in or benefit these patient populations.
3. Patients in the ENGAGE and EMERGE clinical trials were required to undergo a battery of cognitive testing and – with a knowledgeable informant – interviews with an investigator that informed the investigators’ judgement as to whether a subject had mild cognitive impairment (MCI) or mild dementia stage of AD. Cognitive tests used in the trials included the Clinical Dementia Rating (CDR) Scale global score of 0.5, a Mini-Mental Status Examination (MMSE) score between 24 and 30, and a Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) score of 85 or lower. Unfortunately, the FDA-approved label contains no requirement for any specific type of cognitive testing and only refers to patients with "mild cognitive impairment" or "early stage of dementia" and staging of cognitive impairment can be operationalized very differently in clinical practice than in research settings. Notably, the CDR is not routinely used in clinical practice.
4. Patients in both trials were required to have a brain positron emission tomography (PET) scan that was positive for beta amyloid as a criterion for enrollment. However, the FDA label contains no requirement for any testing to assure that patients have beta amyloid before starting aducanumab.
5. In the clinical trials, Amyloid-Related Imaging Abnormalities (ARIAs) monitoring methods and data collection included a centralized MRI reader staffed with radiologists highly experienced with ARIA. ARIAs are divided in two categories – "ARIA-E" for brain edema or effusion and "ARIA-H" for hemosiderin deposits. Patients with mild asymptomatic ARIA could continue aducanumab with caution. For patients with moderate or severe asymptomatic ARIA, any symptomatic ARIA, or radiographically moderate or severe ARIA-E regardless of whether symptoms were present, dosing was suspended until the findings resolved. Participants could resume treatment at the same dose following resolution unless they experienced radiographically severe ARIA-H in which case treatment was permanently suspended. The FDA label requires a pre-administration MRI and follow up MRIs before the seventh and twelfth

doses but does not require suspension of treatment if an MRI shows ARIAs even though treatment was suspended in the trials – unless it was mild asymptomatic ARIA – until ARIA was resolved. The FDA label indicates that if radiographic severe ARIA-H is observed, treatment may be continued with caution only after a clinical evaluation and a follow-up MRI demonstrates radiographic stabilization (i.e., no increase in size or number of ARIA-H). For ARIA-E or mild/moderate ARIA-H, treatment may continue with caution. If dosing is temporarily suspended, dosing may resume at that same dose and titration schedule. There are no systematic data on continued dosing with aducanumab following detection of radiographically moderate or severe ARIA.

We believe that there are many questions that need to be answered about the safety and clinical effectiveness of aducanumab in the real world which will require collection of real-world evidence as a part of any coverage determination by CMS.

Recommendations

Evidence Development

- The CMS NCD must require longitudinal data collection in order to ensure that CMS understands how aducanumab is being prescribed and administered in the real world (e.g., to understand who is getting the product). This is particularly important given the lack of trial data from the following patient populations:
 1. Underrepresented, disproportionately affected, and understudied populations (e.g., Black people living with AD);
 2. People living with AD who were excluded from the Phase 3 clinical trials:
 - People over the age of 85;
 - Patients with other concurrent or previous neurologic pathophysiology (e.g., psychiatric disorders, neurodegenerative disorders, history of stroke, Parkinson’s disease); and
 - People who are on anti-coagulation therapy.

Eligible Patient Population

- CMS should cover the diagnostic testing that is needed to confirm: (1) a diagnosis of MCI or mild stage AD; and (2) the presence of amyloid plaque in the brain assessed using validated methods and interpretive algorithms. The aducanumab NCD should only cover patients who meet the following criteria:
 - Have a diagnosis of MCI or mild stage AD that has been confirmed by neurologic/neurocognitive examination, similar to that required in the Phase 3 clinical trials; and
 - Presence of beta amyloid in the brain confirmed by a positive beta amyloid PET scan, tau PET scan, and/or CSF testing before initiating treatment. Although the trials required a beta amyloid PET scan, the AGS believes that to ensure equitable access to testing, CMS should approve an expanded list of validated tests for determining presence of beta amyloid plaque in the brain.

Setting of Care and Monitoring for Adverse Events

- Given the high incidence of ARIA in the Phase 3 trials, CMS should require that it only be administered in settings where clinicians with expertise in monitoring for, assessing, and treating ARIA are available to assess and monitor patients.

- CMS should consider establishing any other specific criteria that sites must meet in order to administer aducanumab safely to people living with AD.
- CMS should establish specific criteria for monitoring, discontinuing, or stopping aducanumab: For patients with moderate or severe asymptomatic ARIA, any symptomatic ARIA, or radiographically moderate or severe ARIA-E regardless of whether symptoms were present, dosing should be suspended until the findings resolve. Patients can resume treatment at the same dose following resolution unless they experienced severe symptomatic ARIA-H in which case treatment should be permanently suspended.

Shared Decision Making

- CMS should require an annual assessment of every patient taking aducanumab and documentation that a shared decision has been made with the patient and/or their caregiver that the benefits of aducanumab still outweigh the risks and that treatment is still aligned with what matters to the patient.

Optimal Care of People Living with Alzheimer’s Disease and Other Dementias

Although it is beyond the scope of this CMS request for input into its coverage analysis for monoclonal antibodies, the AGS believes that it is important for CMS to consider the wide range of services and supports that all people living with AD and other dementias need. In particular, CMS should consider including a requirement in its NCD for aducanumab that patients who are being considered for aducanumab receive a complete assessment and care plan for their MCI or early-stage Alzheimer’s consistent with the requirements for CPT Code 99483:

- Assessment of and care planning for a patient with cognitive impairment, requiring an independent historian, in the office or other outpatient, home or domiciliary or rest home, with all of the following required elements: Cognition-focused evaluation including a pertinent history and examination; Medical decision making of moderate or high complexity; Functional assessment (e.g., basic and instrumental activities of daily living), including decision-making capacity; Use of standardized instruments for staging of dementia (e.g., functional assessment staging test [FAST], clinical dementia rating [CDR]); Medication reconciliation and review for high-risk medications; Evaluation for neuropsychiatric and behavioral symptoms, including depression, including use of standardized screening instrument(s); Evaluation of safety (e.g., home), including motor vehicle operation; Identification of caregiver(s), caregiver knowledge, caregiver needs, social supports, and the willingness of caregiver to take on caregiving tasks; Development, updating or revision, or review of an Advance Care Plan; Creation of a written care plan, including initial plans to address any neuropsychiatric symptoms, neuro-cognitive symptoms, functional limitations, and referral to community resources as needed (e.g., rehabilitation services, adult day programs, support groups) shared with the patient and/or caregiver with initial education and support. Typically, 50 minutes are spent face-to-face with the patient and/or family or caregiver.

Ideally, patients being treated with aducanumab and their caregivers would have ongoing access to an interprofessional care team who will support them in accessing the services and supports that they will need as they move through the stages of AD. The care plan should be revisited at least annually and there should be an ongoing discussion of what matters to the person so that adjustments to treatment, services, and supports can be made over time.

AGS COMMENTS IN RESPONSE TO CMS QUESTIONS

The AGS also reviewed and commented on the questions outlined by CMS in their NCA for Monoclonal Antibodies Directed Against Amyloid for the Treatment of AD below.

1. Which health outcomes are important, and what degree of improvement in them is meaningful for patients receiving treatment?

The AGS believes that the health outcome goals of treatment and care for patients with AD are to achieve and maintain cognitive and functional stability to the maximum extent possible. Older persons with cognitive impairment – MCI or early-stage dementia – are most often managing a number of concurrent chronic medical conditions. While their cognitive impairment may be the dominant comorbidity, treatment outcomes need to consider the whole person, not isolated disease outcomes. Geriatrics health professionals focus on the 5Ms of geriatrics: **M**ultimorbidity, **W**hat **M**atters, **M**edication, **M**entation (cognitive function), and **M**obility (physical function).¹ Multimorbidity describes the older person who has more complex needs often due to multiple chronic conditions, frailty, and/or complex psychosocial needs. What Matters, Medication, Mentation, and Mobility describe the four main areas where geriatrics health professionals focus their clinical attention and form the basis for the age-friendly health systems framework that is focused on ensuring that all older people have access to this type of coordinated care, while also making sure personal needs, values, and preferences are at the heart of that care.²

In order to have meaningful improvement for patients, crucial health outcomes to consider include reduced symptom burden, effects on cognition and physical function, and sustained health-related quality of life. Cognitive function and physical function are especially important to older adults as reflected in conceptual models for what matters most to older adults such as the 5Ms.³ Sustained daily function at baseline or better would be defined using standardized instrumental activities of daily living (IADL) and activities of daily living (ADL) measures, and sustained quality of life would be defined using a person-centered method in addition to standardized quality of life measures.

We also believe that spouses, family members, and/or caregivers – in addition to patients – should be considered so that the level of anxiety regarding their concern over the loss of memory and/or function in the patient is reduced. It would be important to sufficiently manage co-occurring medical conditions as well as ensure there is no increased risk of unscheduled acute health care needs. The AGS recommends the review of “Dementia prevention, intervention, and care: 2020 report of the Lancet Commission,” a report of individual and policy changes to delay the onset of and provide better ways to support and treat people with cognitive impairment and dementia and their families to improve their quality of life.⁴

¹ Adapted by the American Geriatrics Society (AGS) with permission from “The public launch of the Geriatric 5Ms” [on-line] by F. Molnar and available from the Canadian Geriatrics Society (CGS) at <https://canadiangeriatrics.ca/2017/04/update-the-public-launch-of-the-geriatric-5ms/>.

² Institute for Healthcare Improvement. Age-Friendly Health Systems: Guide to Using the 4Ms in the Care of Older Adults. Available at http://www.ihl.org/Engage/Initiatives/Age-Friendly-Health-Systems/Documents/IHIAgeFriendlyHealthSystems_GuidetoUsing4MsCare.pdf. Published July 2020.

³ Tinetti M, Huang A, Molnar F. The Geriatrics 5M's: A New Way of Communicating What We Do. *J Am Geriatr Soc*. 2017;65(9):2115. <https://doi.org/10.1111/jgs.14979>.

⁴ Livingston G, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet*. 2020;396(10248):413-446. [https://doi.org/10.1016/S0140-6736\(20\)30367-6](https://doi.org/10.1016/S0140-6736(20)30367-6).

2. What characteristics of patients with Alzheimer’s disease are important to optimizing the likelihood of positive health outcomes from treatment?

There is insufficient publicly available data on what characteristics of patients living with AD are important to optimizing the likelihood of positive health outcomes from treatment with aducanumab. FDA approval for aducanumab was based on the surrogate endpoint: reduction of beta amyloid plaque in the brain.⁵ However, as ICER has reported:

“The CDR-SB results from ENGAGE and EMERGE appear to be discordant. In ENGAGE, there was no treatment benefit observed in either the high- or low-dose arms at week 78 (Table 3.2 on the following page). A statistically significant difference in change from baseline in CDR-SB was observed in the high-dose arm of EMERGE (difference vs. placebo -0.39 [95% CI -0.69 to -0.09]), but not the low-dose arm. Although statistically significant, the change in CDR-SB score in the high-dose group was less than the 1-2 point change that has been suggested as a minimal clinically important difference.”⁶

The AGS prioritizes what matters most to patients, their families, and other care partners who want to know whether a treatment provides clear and important benefits to cognitive and functional ability and other key outcomes. To better understand if aducanumab provides clear clinical benefit, more evidence is needed.

We believe that it is critically important that patients and caregivers be fully informed and engaged in an ongoing process of shared decision-making about aducanumab treatment. Additionally, we believe the following considerations are important in order to optimize the likelihood of positive health outcomes from treatment, particularly aducanumab:

- Confirm diagnosis of MCI or mild stage AD supported by a neurologic/neurocognitive examination.
- Confirm presence of beta amyloid in the brain confirmed by a positive a positive beta amyloid PET scan, tau PET scan, and/or CSF testing.
- Establish specific criteria for monitoring, discontinuing, or stopping aducanumab. Such measures are of particular importance for patients who were excluded from the clinical trials (e.g., those taking anticoagulant or anti-platelet medication).
- Collect data on the safety and effectiveness of aducanumab in underrepresented, disproportionately affected, and understudied populations.

⁵ Food and Drug Administration (FDA). *FDA’s Decision to Approve New Treatment for Alzheimer’s Disease.*; 2021. Available at <https://www.fda.gov/drugs/news-events-human-drugs/fdas-decision-approve-new-treatment-alzheimers-disease>.

⁶ Lin GA, et al. Aducanumab for Alzheimer’s Disease: Effectiveness and Value; Draft Evidence Report. Published May 5, 2021. Available at https://icer.org/wp-content/uploads/2020/10/ICER_ALZ_Draft_Evidence_Report_050521.pdf.

3. What issues of equity and inclusion must be accounted for in the diagnosis and treatment of Alzheimer’s disease?

The low rates of specialty dementia care among people of color⁷ and lack of access to clinicians and PET scans in rural and poorer urban areas are significant factors when considering equitable and inclusive patient access to dementia diagnosis, treatment, and care.

Among the barriers to accessing diagnosis and treatment of AD— particularly for people who are socioeconomically disadvantaged – is transportation to appointments. Individuals still working or their family caregivers may need to take time off from their jobs, often lack family and medical leave, and are paid hourly. The AGS encourages the distribution of waivers to assure paid-time off and transportation supports access to diagnosis and treatment.

Early-onset dementia in people less than 65 years of age is approximately one-twentieth as common as later-onset dementia⁸ and among those diagnosed with dementia in the United States, only three percent are individuals younger than 65.⁹ Some of these individuals have AD, and some have other dementing diseases that do not have amyloid pathophysiology. Among those with amyloid pathophysiology, clinical trajectories and other features of disease may differ from the late-onset individuals studied in the pivotal trials and lead to significant differences in response and adverse events. In addition, although younger people with dementia can become Medicare-eligible on the basis of disability, the stages of AD represented in the pivotal trials are too mild to meet the level of disability required for eligibility. The AGS recommends that CMS explore and implement strategies to ensure access to the treatment for individuals on Medicaid who are not yet at the age to be eligible for Medicare.

4. What health care providers should be included as part of the patient’s treatment team? Should medical specialists be included in the care team of patients receiving treatment? If so, which specialists should be included in the care?

We believe this therapy poses particularly high risks and management challenges and prescribers should be competent in dementia care. While cognitive specialists and clinicians with geriatrics expertise may be ideal, we acknowledge that this may unduly limit access. It is essential that prescribers have ongoing management of the patient including dementia care beyond the infusions. CMS may wish to consider a certification process for prescribers and treatment managers. These requirements would address the key elements of capacity to evaluate patients for therapy, administer the infusions, evaluate adverse events (with a focus on ARIA) and amend treatment plans. Access to high resolution MRI scanners and radiological expertise will also be necessary to ensure appropriate monitoring of amyloid deposition in the brain and for ARIA-related side effects.

⁷ Drabo EF, et al. Longitudinal analysis of dementia diagnosis and specialty care among racially diverse Medicare beneficiaries. *Alzheimer’s & Dementia*. 2019;15(11):1402-1411. <https://doi.org/10.1016/j.jalz.2019.07.005>.

⁸ Alzheimer’s Association. 2020 Alzheimer’s disease facts and figures. *Alzheimers Dement*. 2020;16(3):391-460. <https://doi.org/10.1002/alz.12068>.

⁹ Hendriks S, Peetoom K, Bakker C, et al. Young-Onset Dementia Epidemiology Study Group. Global prevalence of young-onset dementia: a systematic review and meta-analysis. *JAMA Neurol*. <https://doi.org/10.1001/jamaneurol.2021.2161>.

To optimally care for persons living with AD, patients should have access to an interprofessional care team that includes health professionals with expertise in primary care, dementia care, nursing, social work, and pharmacy. The clinicians involved should be familiar with the patient and involved in their routine health care and social support needs.

5. In what setting(s) should treatment and care be given?

The treatment setting describes the treatment team capacity. For patients receiving aducanumab, the treatment setting should monitor the patient’s status closely, including for drug side effects. Thirty to forty percent of participants in the Phase 3 trials developed ARIA, a potentially serious adverse event that includes cerebral edema and microhemorrhages. Patients who are actively receiving monthly aducanumab infusions will require close follow-up care to monitor for ARIA-related symptoms and ensure that the FDA-prescribed follow-up MRI scans are obtained and read by radiologists with expertise in ARIA.

Patients receiving aducanumab will also require appropriate monitoring of cognitive and everyday function at specified intervals to assist in determining whether the patient is benefitting from treatment and, if not, to help decide whether to terminate treatment using shared decision-making. At a minimum the ordering clinician(s) must be competent in dementia care. Ideally, the patient’s care team will be interprofessional, inclusive of cognitive specialists and clinicians with geriatrics expertise, so that the patient receives whole person care that is focused on what matters to them. The clinicians involved should be familiar with the patient and involved in their routine health care needs and social supports. Ideally, the team would include a social worker, registered nurse, and pharmacist.

MRI and PET scans needed to establish suitability for treatment and to monitor for ARIA should be required to meet scientifically validated standards for interpretation.

Thank you for taking the time to review our feedback and recommendations. Should you have any follow-up questions, please contact Alanna Goldstein at agoldstein@americangeriatrics.org.

Sincerely,



Peter Hollmann, MD
President



Nancy E. Lundebjerg, MPA
Chief Executive Officer