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SUBMITTED ELECTRONICALLY

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

RE: Proposed National Coverage Determination for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (CAG-0046ON)

Dear Ms. Syrek Jensen:

Alzheimer's Disease (AD) takes a heavy toll on patients, their caregivers, and their family members. They need and deserve equitable access to Food and Drug Administration (FDA)-approved treatments that are safe and effective. AHIP[1] supports access to treatments that improve a patient's quality of life and ability to enjoy more valued time with loved ones.

AHIP strongly supports the Centers for Medicare & Medicaid Services' (CMS) Proposed National Coverage Determination (NCD) for Monoclonal Antibodies Directed Against Amyloid for the Treatment of AD. We commend CMS for its comprehensive, thoughtful and objective analysis of the clinical evidence, benefits, and potential side effects of this class of therapies. **We agree with CMS' conclusion that "no trial has been able to demonstrate any meaningful improvement in patient health outcomes,**" noting: "Due to the lack of a clear clinical benefit and the frequency of adverse events like [amyloid related imaging abnormalities] ARIA, the evidence does not support that the benefits outweigh the harms for mAbs directed against amyloid for the treatment of AD."

Yet, given the importance of finding treatments for this devastating disease and what CMS characterized as the "potential for promise with this treatment," we also support CMS' proposal to provide Medicare coverage in the context of clinical trials that:

- can facilitate collection of additional evidence with a consistent approach,
- require the products in this therapeutic class be administered by clinicians experienced in caring for patients with AD so they can closely monitor and manage the potentially serious adverse events that may occur, and
- ensure evidence development of safety and efficacy includes diverse populations.

The proposed NCD is the right approach for patients. It would provide Medicare patients consistent and national access to this class of products and related services. And it would

[1] AHIP is the national association whose members provide health care coverage, services, and solutions to hundreds of millions of Americans every day. We are committed to market-based solutions and public-private partnerships that make health care better and coverage more affordable and accessible for everyone. Visit www.ahip.org to learn how working together, we are Guiding Greater Health.

appropriately emphasize the need for sufficient clinical evidence to support future determinations of whether these drugs are both reasonable and necessary for the right populations within the program. We provide more detail below in support of key elements of the proposed NCD and identify additional issues for CMS' consideration and clarification as you work to finalize the NCD.

Coverage with Evidence Development (CED) in Clinical Trials

Under section 1862(a)(1)(A) of the Medicare Act, the Medicare program may cover a new product only if CMS determines the product is "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." Thus, in order to approve coverage, the statute would require CMS to reach a definitive and independent evidentiary conclusion that the product has actual clinical benefits in treating AD based on the evidence available today. It would also require that CMS assess any benefits against the known safety risks for Medicare patients.

After reviewing over 250 peer-reviewed documents relevant to the NCD analysis, as well as reports from other agencies, the Institute for Clinical and Economic Review (ICER), public comments, feedback from two broad-based stakeholder meetings, and numerous meetings with individual stakeholders, CMS concluded that there is *"*insufficient evidence to conclude that the use of monoclonal antibodies directed against amyloid is reasonable and necessary for the treatment of Alzheimer's disease." As CMS indicates in its discussion of evidence in the proposed decision memo, the assessment focused on the key question of whether the use of monoclonal antibodies directed against amyloid for the treatment of AD improves health outcomes for people covered by Medicare. Moreover, the standard is not simply "*could* this class of drugs be helpful to patients with AD," but rather an additional determination must be made that it is "necessary" for them to access these treatments. Again, we agree with CMS that this secondary standard is not met until sufficient clinical evidence supporting the efficacy of this class of drugs in treating AD is developed.

Following its review of the quality and strength of evidence, CMS concluded that *"*there is some preliminary research that shows promise, but it's far from conclusive and more rigorous individual trials (i.e., RCTs) continue to be needed to determine the clinical benefit of antiamyloid mAbs for the treatment of AD.*"* Moreover, in assessing the benefits and harms of the treatment, CMS concluded: *"*Due to the lack of a clear clinical benefit and the frequency of adverse events like ARIA, the evidence does not support that the benefits outweigh the harms for mAbs directed against amyloid for the treatment of AD.*"*

Based on this thorough evidentiary review and because AD is a disease that affects many people with Medicare (many of whom have other underlying chronic conditions), CMS has proposed to cover this class of drugs under a CED paradigm where the treatment is furnished in the context of randomized controlled trials (RCT) meeting CMS-specified criteria and approved by CMS, or trials supported by the National Institutes of Health (NIH). Additionally, all trials must be conducted in a hospital-based outpatient setting.

Comment: We support CMS' proposal to narrowly target coverage within the context of an evidence development process as provided under section 1862(a)(1)(E) of the Medicare Act, which allows CMS to provide coverage for research on a product that otherwise does not meet the "reasonable and necessary" standard. CED in the context of clinical trials will facilitate collection of additional evidence in the near term to better inform refinement of coverage conditions for this class of drugs in the future. It will also help ensure that clinicians with experience in caring for patients with AD will be involved in the administration of this class of medication and allow for closer monitoring and management of adverse events.

We support the use of rigorous clinical studies. The approved clinical trials should be double-blinded, randomized, and case controlled. Such trials are the recognized "gold standard" for assuring unbiased results that evaluate the efficacy of the drug independent of factors that may otherwise influence patient experience and interfere with efforts to understand the role of the studied drug in determining clinical outcomes. The use of less rigorous methods, such as registries, would not allow CMS to draw additional conclusions on the clinical efficacy of this class of drugs.

Additionally, we support CMS' proposal to apply this NCD to the entire class of antiamyloid-beta monoclonal antibodies (antiamyloid mAb) rather than a specific drug, given that there are at least three other antiamyloid mAbs currently approaching Phase 3 trials, in addition to the one treatment currently approved by the FDA (aducanumab) under the accelerated approval pathway. Of notable significance, CMS has the flexibility to revisit this NCD and reassess coverage policies for the Medicare program as the evidence evolves -- if and when a drug in this therapeutic class obtains FDA approval and shows clear evidence of clinical benefit to patients and is demonstrated to be safe.

Patient Clinical Trial Eligibility Criteria

The proposed NCD includes patient inclusion criteria that are similar to those in the premarket approval trials and the revised FDA approved label for aducanumab. Namely, eligible patients include those with mild cognitive impairment due to AD or mild AD dementia and who show evidence of amyloid pathology consistent with AD. Furthermore, under the proposed NCD, eligible patients must not have any other medical or neurological condition (other than AD) that could contribute to the individual's cognitive impairment or that are likely to increase significant adverse events.

Comment: We agree that CMS' CED framework should be targeted to patients most aligned with the inclusion and exclusion criteria applied to the population studied in the clinical trials and support CMS' proposal to apply its coverage policy to populations consistent with the FDA approved label. Accordingly, CMS should consider the additional

aducanumab Phase 3 clinical trial inclusion and exclusion criteria in its evaluations of clinical trial proposals under this NCD.[2]

We also recommend that the eligibility criteria exclude patients previously in a clinical trial for a drug in the same class, both to avoid evidence assessment complexities and ensure trials are accessible to as many patients as possible. Enrolling in multiple consecutive trials or switching trials mid-study for reasons other than trial discontinuation or consolidation with another CMS-approved or NIH-supported trial would undermine the validity and continuity of any evidence generated by the trials.

Clinical Trial Research Questions on Clinical Benefit and Adverse Effects

Under the proposed NCD, clinical trials must address two research questions: (1) whether the treatment results in a statistically significant and clinically meaningful difference in decline in cognition and function; and (2) what adverse events are associated with the treatment.

As noted in the proposed NCD, substantial questions have been raised about the effectiveness of aducanumab. The FDA's independent expert advisors on the Peripheral and Central Nervous System Drugs Advisory Committee overwhelmingly voted against approval of aducanumab based in large part due to the lack of conclusive evidence of patient benefit presented in the studies. Likewise, significant concerns have been raised about the safety of aducanumab and its FDA-approved label includes warnings regarding the potential for ARIA that could indicate brain edema or brain hemorrhages. Prominent health care systems (including Cleveland Clinic, Mass General Brigham, and Mount Sinai) stated they would not administer aducanumab to their patients given the lack of evidence that it is effective and the clear evidence of potential patient risks.[3]

As we have previously commented, it is critical that evidence be collected on the extent to which the treatment affects clinical and functional outcomes that are important to patients (and their families), including improved cognitive outcomes, low incidence of adverse events, and maintenance or improvement of a patient's overall ability to function, such as improved quality of life, sustained independence, ability to continue with activities of daily living, and reduced caregiver burden, as measured by validated assessment tools. Furthermore, given that available clinical trial data showed that ARIA was observed in 41% of patients treated with aducanumab and one possible related death was being investigated[4], it is essential that the CED framework closely and carefully monitor and track adverse events for the protection of patients participating in the CMS approved clinical trials.

Comment: We support CMS' proposal to require that, in order to receive CMS approval, trials must specifically address, at a minimum, research questions regarding meaningful clinical benefit and adverse events and agree these considerations should be important elements of CMS' conditions of coverage under the CED process. A CED process that collects evidence on clinical benefit and adverse events is critical to CMS' assessment of continued coverage of aducanumab and other drugs in this class and can also provide

[2] For details on inclusion and exclusion criteria, see: https://clinicaltrials.gov/ct2/show/NCT01677572

[3] https://www.statnews.com/2022/01/06/top-hospitals-arent-offering-aduhelm/

[4] https://www.nytimes.com/2021/11/22/health/aduhelm-death-safety.html

information to the FDA to assist in designing the FDA-required confirmatory trial of aducanumab and, if needed, future confirmatory trials for other drugs in this class.

The proposed NCD defers to clinical trial sponsors to identify thresholds for clinical improvement (provided such thresholds are supported by peer reviewed, published medical literature). We recommend that, for these trials, clinical improvement be measured and assessed using validated tools that are standardized and consistent across the trials. Outcomes should have clearly defined scales that are applied consistently to preserve the intent for true and unbiased reporting of results.

Diversity in Clinical Trial Population

In addition to meeting established standards of scientific integrity, the proposed NCD highlights the requirement that the diversity of patients included in each trial be representative of the national population diagnosed with AD.

As noted in our previous comments, the clinical trials conducted by the manufacturer failed to represent the diversity of the 6 million Americans living with AD. The FDA's own guidance on diversity in clinical trials states that participants in trials should represent the patients that will use the medical product. Given the elevated rate of dementia among certain groups, it is critical that proposed RCTs be evaluated for their methods to enroll diverse populations as part of CMS' approval process.

Comment: We strongly support CMS' emphasis on the importance of evaluating the safety and effectiveness of treatment on different groups beyond those enrolled in the clinical trials, including minorities, underserved, and low-income individuals, many of whom are at greater risk for developing AD and who may be more likely to have a missed diagnosis of the disease. Without this additional research, it will be unclear whether access to this treatment, with its accompanying risks, is in the best interests of diverse populations that have been systematically underserved by prior clinical trials. Moreover, a trial population that is representative of the national population diagnosed with AD will promote equitable access to diagnosis and treatment across geographies and groups and enable CMS to evaluate whether the results are generalizable across a broader population.

Given that nearly half of all racial and ethnic minorities eligible for Medicare choose a Medicare Advantage (MA) plan, we look forward to discussions with CMS regarding how MA plans may assist CMS in reaching diverse groups and achieving its goal of representative populations participating in approved clinical trials.

Coverage of Positron Emission Tomography (PET) Scans

The NCD proposes that patients participating in the trials be eligible to receive Medicare coverage of one beta amyloid PET scan if required by the clinical trial protocol and if the patient did not previously receive a PET scan to confirm presence of beta amyloid plaque.

We previously commented that any affirmative coverage decision must address the extent to which such coverage is conditioned on, and the extent to which Medicare will cover, PET scans for the purpose of identifying amyloid plaque prior to or as part of eligibility for the Aduhelm treatment regimen.

Comment: We support CMS' proposal to include coverage of a beta amyloid PET scan if required by the clinical trial protocol to confirm the presence of amyloid beta plaque in patients prior to treatment and/or determine the need for continued treatment. We also note that CMS did not address coverage policies for cerebral spinal fluid as an alternative to a PET scan to confirm amyloid positivity, nor did it address coverage policies for MRIs to screen for potential brain swelling or bleeding or other adverse events based on patient symptoms. Accordingly, we request that CMS confirm that Medicare would cover these services consistent with patient symptoms and in accordance with general CMS clinically appropriate coverage guidelines.

Additional Questions and Areas of Clarification

In addition to the recommendations and considerations raised above, there are several areas that warrant clarification from CMS. These areas include implications for the MA, Medicare Supplemental, and Medicaid programs, as well as considerations regarding patients who are already receiving aducanumab or are participating in one of the currently ongoing phase 3 or 4 trials being conducted on other drugs in this class. In particular:

- We request that CMS' Office of the Actuary provide to the public a determination of whether the NCD would meet the requirements of section 1852(a)(5) of the Social Security Act for plan year 2022 as quickly as possible after the final NCD is released. Under that statutory provision, if CMS determines that an NCD would result in a significant change in costs, Original Medicare is required to assume the costs covered by the NCD for MA enrollees until the plan year for which the expected costs are appropriately reflected in MA benchmarks. CMS should also evaluate whether costs associated with the NCD as finalized are appropriately included in benchmarks for purposes of section 1852(a)(5) for plan year 2023. In addition, we note the need for re-evaluation in the future, given the additional treatments under development in this class.

- We also request that CMS provide clear guidance to MA plans on their coverage obligations under the NCD. Key issues that should be addressed include CMS maintaining an updated list of all clinical trials that meet the proposed requirements under the CED pathway and making it publicly available to MA plans and other stakeholders; plan obligations for coverage of and payment for such trials, including coverage of aducanumab, placebos, and any ancillary treatments or services considered part of a clinical trial; and flexibility for medical management in the event an RCT is extended to a longitudinal study (i.e., registry).

- In addition to addressing MA plan responsibilities under the NCD, we urge CMS to provide information and guidance to Medicare Supplement carriers that explains the cost sharing amounts associated with care provided as part of the Medicare-covered clinical trials along with estimated enrollment, duration, and costs of such trials to ensure carriers are able to meet financial obligations.

- We support CMS' coverage decision for the Medicare program, but we share the concerns of some commenters about the potential impacts for state Medicaid programs that may be required to cover aducanumab and other products in this class for people dually eligible for Medicare and Medicaid. We urge CMS to clarify what types of medical necessity

criteria and other flexibilities may be available to state Medicaid programs for these treatments.

- Additionally, we ask that CMS clarify its expectations regarding coverage for people with Medicare who are already receiving aducanumab, as well as whether phase 3 and 4 trials currently underway for other drugs in this class meet the criteria of a CMS-approved clinical trial.

- AHIP also urges CMS to ensure there is clear communication on how coverage and payment will occur from patients' and other stakeholders' perspectives (e.g., process for submitting a claim, process for validating patient participation in a qualified clinical trial).

- Lastly, we request that CMS clarify that drugs in this class are Part B products. Such clarification is necessary to make clear CMS' determination that Part D does not cover monoclonal antibodies directed against amyloid for the treatment of AD, regardless of whether such treatments are provided to a Part D enrollee through a clinical trial described in the final NCD, pursuant to the provisions of section 1860D-2(e) of the Social Security Act.

AHIP and its member health insurance providers strongly support Medicare coverage of drugs that show clear evidence of clinical benefit to patients by saving lives, reducing the burden of illness, and improving health and quality of life. We appreciate the extensive and thorough review that CMS undertook in its national coverage analysis process. CMS and many clinicians, health systems, and other stakeholders recognize that Medicare coverage should apply only when there is clear evidence of clinical benefit to patients that outweighs the risk of significant harm, and they have appropriately concluded there is not sufficient evidence on safety and effectiveness to meet this standard.

AHIP supports the proposed NCD framework that would provide coverage for this new class of therapies under CED in the context of RCTs to develop additional evidence on safety and effectiveness for this class of drugs. We strongly agree with CMS' observation that *"*it is appropriate access that matters*"* and we share CMS' concern regarding the *"*potential harms to Medicare patients, especially since patients in these trials have early or mild diseases (MCI or mild AD) and are relatively high functioning." We agree with CMS that: *"*It is important to first demonstrate that the clinical benefits outweigh the harms within the patient protections and controlled settings of RCTs" and urge CMS to finalize its CED paradigm.

We appreciate CMS' consideration of these comments and would be happy to answer questions or provide additional information upon request.

Sincerely,

Matthew Eyles