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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
ATTN: NCDRequest@cms.hhs.gov

RE: **National Coverage Determination Analysis for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease**

Dear Ms. Syrek Jensen:

Alzheimer's disease takes a heavy toll on patients, their caregivers, and their family members. They need and deserve access to Food and Drug Administration (FDA)-approved treatments that are safe, effective, and equitable for this irreversible, progressive, and debilitating disease. As the national association whose members provide health care coverage, services, and solutions to hundreds of millions of Americans every day, 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') decision to initiate a National Coverage Determination (NCD) analysis for treatment of people with Alzheimer's disease with monoclonal antibodies directed against brain amyloid. We appreciate CMS' willingness to undertake a careful analysis of the clinical evidence, benefits, and potential side effects of this class of therapies. CMS' establishment of a consistent national approach to Medicare access to these products and related services is imperative given the unique combination of challenges the FDA's approval has created. Moreover, there is intense interest in aducanumab's approval by the FDA and the precedent it may set regarding other new products, which further increases the need for clarity around Medicare coverage.

While the FDA's approval of aducanumab (marketed as Aduhelm™) for the treatment of Alzheimer's disease under the accelerated approval pathway clearly provides hope for people desperate for new treatment options, aducanumab is not a cure. In fact, significant uncertainty remains regarding whether it has any impact addressing either current symptoms or the progression of the disease. FDA's approval was based on the surrogate endpoint of the reduction of amyloid beta plaque in the brain that is expected to predict clinical benefit. However, the clinical trials found no clinical benefits from reducing that plaque and revealed serious safety risks to patients receiving the monthly infusions of aducanumab including swelling and bleeding in the brain. Accordingly, as discussed below, aducanumab currently does not appear to meet the statutory requirements for Medicare coverage of products that are "reasonable and necessary" for treatment.

[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.

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 Alzheimer's disease based on the evidence available today. It would also require that CMS assess any benefits against the known safety risks for Medicare patients.

This statutorily governed coverage determination standard may be satisfied following FDA approval of a drug under the standard pathway based on evidence of clinical benefit and safety for patients in clinical trials. In the case of a product approved under FDA's accelerated pathway, CMS could determine a product is reasonable and necessary without direct evidence of clinical benefit if the product shows clear potential for clinical benefit through improvement in a surrogate endpoint that is known to improve health or functioning.

In the case of aducanumab, however, CMS has direct evidence that the drug lacks clinical benefit, as shown by two failed clinical trials, both of which were stopped because the drug did not help patients. In addition to the clear evidence from those trials of aducanumab not offering clinical benefit to patients, there is documented risk of harm to patients from aducanumab. The clinical trials for aducanumab caused a substantial proportion of patients to experience brain swelling or brain bleeding, both of which carry significant safety risks. The FDA Advisory committee and numerous other clinical and scientific experts reviewed the available evidence and concluded that aducanumab has demonstrated serious risk of harm for patients but has not demonstrated clinical benefit. Given these compelling data points, it does not appear that CMS can conclude that the treatment is "reasonable and necessary" as required by the statute based on currently available evidence.

Despite the safety risks and uncertain clinical efficacy, if CMS determines under the statutory framework that aducanumab qualifies for Medicare coverage in some circumstances, we urge the agency to narrowly target coverage within the context of an evidence development process as provided under section 1862(a)(1)(E) of the Medicare Act. That provision allows CMS to provide coverage for research on a product that otherwise does not meet the "reasonable and necessary" standard discussed above. This process can facilitate collection of additional evidence in the near term to better inform refinement of coverage conditions in the future. Any such coverage should apply to populations consistent with those in the clinical trials. It would also need to address the related services that are necessary to accurately identify patients for whom treatment with aducanumab would be appropriate, monitor them for harmful side effects, and identify the conditions under which coverage may no longer be appropriate for a given patient (e.g., discontinuation of treatment).

We urge CMS to issue an NCD as swiftly as possible. In the interim, we ask CMS to consider providing guidance that reaffirms Medicare Advantage (MA) plans' flexibility to determine whether and under what circumstances coverage of aducanumab is reasonable and necessary in the absence of an NCD. We also request that CMS ensure any coverage decision determined to be "reasonable and necessary" under the statute is accompanied by a timely acknowledgement that aducanumab meets the "significant cost threshold" under the Medicare statute. Original Medicare should assume risk for the costs of aducanumab until the MA plan year for which the expected costs of aducanumab are appropriately reflected in MA benchmarks.

We provide more detail below on these comments, along with feedback on the specific questions CMS raised in the announcement of the NCD analysis. We appreciate CMS' consideration of these comments and would be happy to answer questions or provide additional information upon request.

Sincerely,

Matthew Eyles
President & Chief Executive Officer

Review of Clinical Benefits and Patient Harm

Substantial concerns have been raised about the safety and effectiveness of aducanumab. These considerations should be important elements of CMS' assessment of whether the therapy satisfies the "reasonable and necessary" standard in the Medicare statute.

- FDA Panel. The FDA's independent expert advisors on the Peripheral and Central Nervous System Drugs Advisory Committee overwhelmingly voted against approval of aducanumab. One of the key conclusions highlighted by the independent experts on the FDA Advisory Committee was the lack of conclusive evidence of patient benefit presented in the studies.
- Efficacy Data. As noted above, aducanumab's efficacy was not demonstrated through a typical clinical endpoint such as a cure or halting progression of Alzheimer's disease, but rather through a surrogate endpoint of reducing amyloid beta plaque[2] which has not been conclusively proven to achieve clinical benefit for patients in clinical trials. There is no scientific consensus on whether amyloid plaque is a causative agent of Alzheimer's disease or whether plaque reduction results in reduced cognitive decline. The FDA approval did not determine that the product is effective in addressing the cognitive impacts of Alzheimer's disease or improving or limiting cognitive decline. Clinical and cognitive measures of patient benefit are critical in CMS' assessment of whether a product is reasonable and necessary under the Medicare statute, as compared to merely being an experimental product that is outside of Medicare's ordinary coverage rules.

- Safety Risks. The publicly available clinical trial data, though not published in a peer-reviewed journal, identified serious safety risks for patients treated with aducanumab. Aducanumab's FDA-approved label includes the following warnings: "ADUHELM can cause amyloid related imaging abnormalities (ARIA)-edema (ARIA-E), which can be observed on MRI as brain edema or sulcal effusions, and ARIA hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis." Notably, in Studies 1 and 2 ARIA (-E and/or -H) was observed in 41% of patients treated with aducanumab with a planned dose of 10 mg/kg (454 out of 1105), compared to 10% of patients on placebo (111 out of 1087). As patients start receiving this treatment in real world settings rather than in the controlled setting of clinical trials, higher risk patients may experience even more adverse outcomes that may not be identified early if MRIs do not occur as frequently. Further, in assessing whether a new therapy is reasonable and necessary, safety risks should be considered not only by themselves, but in the context of the evidence of potential clinical benefits – or in the case of aducanumab, the lack of evidence of cognitive improvements or limits on cognitive decline. That is, with the known risks and unclear benefits of aducanumab based on the clinical trial evidence, CMS can deem the therapy not "reasonable and necessary" under the Medicare statute.

- Value Assessment. The Institute for Clinical and Economic Review (ICER) determined that

[2] Even if relevant to the reasonable and necessary standard under the Medicare statute, this outcome was subject to conflicting and inconclusive evidence.

the clinical-trial evidence is "insufficient" to show a net health benefit for patients with mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease. Additionally, ICER noted that "if we rated the net benefit for the entire population of individuals with Alzheimer's disease specified in the FDA label, our evidence rating would likely have been lower: for the population of patients with severe Alzheimer's disease, it is reasonably likely that aducanumab's harms outweigh any potential evidence." A panel from the California Technology Assessment Forum (CTAF), a nationally recognized independent committee of medical evidence experts that engages clinicians, patients and payers, convened a public meeting on July 15, 2021, during which they reviewed the ICER report and voted unanimously that the evidence shows that aducanumab does not provide any more clinical benefit than routine care.[3]

Considerations of Coverage with Evidence Development (CED)

While we do not believe CMS can conclude that aducanumab meets the Medicare coverage standard based on the risk of serious beneficiary harm and the lack of clinical benefit, we recognize that even if CMS agrees, CMS may still consider other statutory approaches that permit some degree of coverage under the Medicare program. In that context, an available approach under the Medicare statute would be for CMS to approve coverage only in connection with a CED process. As CMS has previously noted, an NCD involving CED is appropriate when CMS decides after a formal review of the medical literature that it will cover an item or service only in the context of an approved clinical study or when additional clinical data are collected to assess the appropriateness of an item or service for use with a particular beneficiary.[4] Such coverage is permissible under section 1862(a)(1)(E) of the Social Security Act, which allows CMS to provide coverage for research on a product that otherwise does not meet the "reasonable and necessary" standard of section 1862(a)(1)(A).

CMS has developed a variety of principles and requirements for CED studies[5], one of which provides that "the rationale for the study is well supported by available scientific and medical evidence." Given the serious safety risks and the lack of demonstrated clinical benefit described above, it is unclear whether a CMS-covered clinical trial of aducanumab would meet that standard. However, if CMS determines it is appropriate to move forward with CED for aducanumab or similar products, CMS should ensure the study is designed to meet the previously articulated principles and requirements. They include ensuring that the study protocol explicitly discuss beneficiary subpopulations affected by the item or service under investigation, particularly traditionally underrepresented groups in clinical studies.

One of the important considerations of a CED for aducanumab is that the FDA label provides that "[c]ontinued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s)." However, the Phase 4 confirmatory trial(s) are not expected to be completed until 2029, with submission to the FDA in 2030. Coverage with evidence development would allow development of additional evidence sooner rather than later and can provide information to the FDA in designing the confirmatory trial that the manufacturer is required to conduct. Accordingly, if CMS provides some degree of coverage under Medicare, CMS should ensure data is collected on patients with Medicare coverage regardless of any other conditions associated with the coverage, such as through creation of a registry or other mechanism. This will enable the capture of consistent

[3] Information available at: https://icer.org/assessment/alzheimers-disease-2021/

[4] See: Guidance for the Public, Industry, and CMS Staff: Coverage with Evidence Development, available at: https://www.cms.gov/medicare-coverage-database/details/medicare-coverage-document-details.aspx?MCDId=27

[5] *Id*.

information on the status, progress, side effects and outcomes of these patients through the entire course of their treatment.

Feedback on CMS Questions

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

Given the lack of evidence that a reduction in amyloid plaque results in clinical benefit to patients with Alzheimer's disease, a reduction in amyloid plaque alone should not be considered a meaningful health outcome for Medicare beneficiaries. To determine that aducanumab or similar treatments meet Medicare's statutory standard for coverage that a product is "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member," CMS should be able to conclude that the evidence shows the potential for both clinical and functional outcomes that are important to patients, including:

- Improved cognitive outcome as evidenced by halting or slowing the progression of disease. Objective assessment of cognitive outcomes should be based on standardized and validated assessment tools, such as the Clinical Dementia Rating (CDR) Scale – Sum of Boxes (CDR-SB), Mini-Mental State Exam (MMSE), and/or Montreal Cognitive Assessment (MoCA).
- Low incidence of adverse events, including ARIA and mortality rate.
- Maintaining or improving overall ability of the patient 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.

Should CMS provide coverage through a CED process, coverage should be contingent on achieving these and additional clinical and functional outcomes. It will also be critical for CMS to lead a process by which patients, providers, payers, and policymakers reach consensus on a consistent process for tracking clinical and functional outcomes over time, with interim results to build a full understanding of the impact of this treatment and the ability to compare the clinical impacts of other similar treatments as more become available.

Lastly, when CMS is considering health outcomes for coverage purposes, key questions remain over the appropriate dosing and duration of treatment. Despite the fact the two Phase 3 clinical trials of aducanumab were discontinued, one trial showed that some effect on amyloid beta plaque was realized by patients at higher doses. Therefore, it will be important for CMS to carefully consider what dosing level is needed to achieve the identified outcomes. The NCD should also address whether continued treatment is contingent upon improvement in clinical and functional outcomes and how long it will cover treatment given potentially dangerous side effects. These kinds of important assessments are usually completed during FDA's review process of new drugs and biologics, but they remain unanswered under the accelerated approval provided for aducanumab.

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

The original labeling approved by the FDA for aducanumab applied to the treatment of patients with all stages of Alzheimer's disease. On July 8, 2021, the FDA revised its approved usage labeling for aducanumab to indicate that treatment with aducanumab "should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied."

If CMS determines that this treatment is appropriate for coverage under statutory criteria in the context of a CED process, such coverage should not simply follow the updated approved label. Rather, it should be targeted to beneficiaries most aligned with the inclusion and exclusion criteria applied to the population studied in the clinical trials[6]. Those criteria include, but are not limited to:

- Diagnosis of mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease dementia including appropriate scores on standardized and validated assessment tools (e.g., a CDR global score of 0.5 or an MMSE score between 24 and 30 or the equivalent MoCA score)
- Validation of presence of amyloid plaque since that is what the treatment addresses (even though evidence on plaque as a causative factor for Alzheimer's disease is inconclusive)
- No other medical or neurological condition that might be a contributing cause of the individual's cognitive impairment (e.g., co-morbid vascular dementia/MCI)
- No clinically significant psychiatric illness within the past 6 months
- No history of bleeding disorder (e.g., based on a baseline MRI, within the past year, that does not show localized superficial siderosis, four or more brain microhemorrhages, or brain hemorrhage greater than 1 cm)
- Not on antiplatelet or anticoagulant therapy

In addition, if CMS determines that the treatment meets statutory criteria for coverage, Medicare beneficiaries must have access to needed scans and assessments to determine if they meet the target population criteria, to determine the presence of amyloid plaque, to monitor adverse reactions, and to assess progress. They also must be willing to undergo these scans and other evaluations on a frequent basis to regularly assess progress. Patients may need assistance with transportation and other support in order to participate in and adhere to the necessary treatment regimen. Thus, any affirmative coverage decision must address the extent to which such coverage is conditioned on, and the extent to which Medicare will cover, Positron Emission Tomography (PET) scans for the purpose of identifying amyloid plaque prior to or as part of eligibility for the Aduhelm treatment regimen[7]; coverage and frequency of cerebrospinal fluid (CSF) sampling as an alternative to PET scans to screen patients for the presence of amyloid; and coverage of magnetic resonance imaging (MRI) scans to monitor for brain swelling or bleeding and other adverse events. We suggest that CMS consider at least the following questions:

- Will CMS re-open the PET scan NCD and/or require and cover a baseline PET scan to confirm the presence of amyloid beta plaque in patients prior to being eligible to be treated with Aduhelm?
- Will PET imaging to detect amyloid beta plaque be required for coverage of continuing treatment consistent with the clinical trials for the drug (e.g., confirmation relating to amyloid beta plaque)?
- Based on Medicare's ongoing CED requirement for use of PET imaging, will Original Medicare continue to deny coverage requests for routine clinical use of PET scans to detect amyloid beta plaque if ordered by the prescribing physician prior to starting a patient on Aduhelm?
- Will Cerebrospinal Fluid (CSF) testing for amyloid beta plaque be covered as an alternative to the amyloid PET?
- Should CMS decide to cover PET scans, please consider scenarios such as one time use to establish the diagnosis of Alzheimer's disease, diagnosis for other indications, management of patients on Aduhelm to assess response to therapy, screening asymptomatic patients at risk for Alzheimer's disease.

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

[7] Alternatively, will Original Medicare continue to deny coverage requests for routine clinical use of PET scans to detect amyloid beta plaque if ordered by the prescribing physician prior to starting a patient on Aduhelm?

Given the difficulty of the treatment, it will be important for a proficient clinician to assess the patient's willingness and ability to adhere to the regimen of monthly infusions, in addition to the regular follow-up scans to track progress and monitor for adverse events and other appointments, examinations, and assessments as needed. Further, patients must have the ability to make an informed decision regarding their treatment, given the significant uncertainties regarding the benefit and the risk of serious side effects. CMS also will need to consider what to do if a patient cannot tolerate the treatment and discontinues therapy and decides to try again, i.e., will CMS cover the treatment a second time for the same patient.

Unfortunately, the clinical trials conducted by the manufacturer failed to represent the diversity of the 6 million Americans living with Alzheimer's. Therefore, in considering the components of a potential CED determination, it is critical that CMS require research to evaluate the safety and effectiveness of the treatment on different sub-populations beyond those enrolled in the clinical trials, including minorities and underserved populations.

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

As mentioned above, due to the lack of diversity in the clinical trial population and the inability to generalize the results across a broader population, more research is needed to evaluate the safety and effectiveness of the treatment on different sub-populations before making coverage available beyond the population aligned with the trials. Without this additional research, it is unclear whether access to this treatment with its accompanying risks would be in the best interests of populations that have been systematically underserved or ill served by prior clinical trials, including those for this treatment.

If CMS determines that this treatment meets statutory criteria for coverage, CED can allow for more evidence to be gathered on safety and efficacy across more diverse patient populations, including minorities, underserved, and low-income individuals, many of whom are at greater risk for developing Alzheimer's disease and may be more likely to have missed diagnoses of the disease. It will be important for any CED policy to ensure equitable access to diagnosis and treatment across geographies and sub-populations. This will be especially challenging given the inadequate number of people of color and other minorities included in the clinical trials, which makes it difficult to assess the safety or efficacy of treatment on these populations. In addition, patients in rural and underserved areas may have limited access to the full range of necessary diagnostic testing, radiology studies, neurologists, and other specialists, making equitable access to diagnosis and treatment more difficult.

There are also concerns among many stakeholders that with the high out-of-pocket costs patients on this treatment would be responsible for, only patients with the means to afford those costs will be able to access the treatment and related testing. This will exacerbate longstanding inequities in access to care and cause potential economic hardship to patients who undertake a therapy that has not been shown to deliver clinical benefit.

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?

If CMS determines that the treatment meets statutory criteria for coverage, it is essential that members of the patient's care team be prepared and proficient, not only in the diagnosis of patients who should be eligible for the treatment and administering the infusion therapy, but also in the comprehensive wraparound care that must accompany this treatment, including PET scans and/or cerebrospinal (CSF) testing to confirm the presence of amyloid plaque and MRIs to monitor for adverse events. The care team should consist of providers with expertise and proficiency across all aspects of this treatment, including patient diagnosis, monitoring and managing drug infusion treatment, monitoring and managing treatment complications such as ARIA, and assessing patients'

progress based on clinical and functional outcomes. The care team should use standardized tools to assess the patient's activities of daily living, quality of life and other key factors important to patients on whether to initiate or continue treatment. Care team providers could include:

- Primary care providers
- Neurologists, neuropsychologists, behavioral neurologists
- Geriatricians, geriatric psychiatrists, geropsychologists
- Specialized memory clinics or experienced centers with care teams able to accurately diagnose patients with early Alzheimer's disease, effectively manage potential adverse events, and ensure appropriate follow-up with patients to assess progress.

CMS may wish to consider differentiating the type of providers eligible for making diagnoses versus providers eligible for ordering the treatment, interpreting scans, and monitoring for and managing side effects. The care team should also include members with expertise in shared decision-making and financial counseling to ensure ongoing and candid discussions with patients and their families about the uncertainties and challenges of the treatment, the risks and benefits, options, and other key information. Consistent with CMS' focus on equity, inclusion, and shared decision-making to put individuals at the center of their care, should Medicare provide coverage for Aduhelm, doctors, their patients and caregivers should have thoughtful conversations about the known risks and unclear benefits of the therapy prior to making a treatment decision. It will be particularly important for the patients and their caregivers to understand and acknowledge the significant risks of treatment associated with Amyloid-Related Imaging Abnormalities suggestive of Vasogenic Edema and Sulcal Effusions (ARIA-E) and Hemosiderin Deposits (ARIA-H). The doctor, patients, and their caregivers should also discuss that FDA approval of Aduhelm was based on reduction in amyloid beta plaques without verification of clinical benefit.

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

If CMS determines that the treatment meets statutory criteria for coverage, there should be the flexibility for care to be delivered in settings that are safe, convenient, and affordable and by providers experienced with administering infusion treatments.