601 Pennsylvania Avenue, NW
South Building, Suite 500
Washington, D.C. 20004

T 202.778.3200
C 202.450.8218
ahip.org

Matthew Eyles
President & Chief Executive Officer

June 30, 2021

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: **A Formal Request for a National Coverage Determination on Aducanumab**

Dear Ms. Syrek Jensen:

On June 7, 2021, the Food and Drug Administration (FDA) approved aducanumab (marketed as Aduhelm™) for the treatment of Alzheimer's disease under the accelerated approval pathway. As a novel amyloid-beta directed antibody indicated to treat Alzheimer's disease, we understand that FDA's approval of aducanumab was based on the surrogate endpoint of the reduction of amyloid beta plaque in the brain that is expected to predict clinical benefit, although no clinical benefit was established by the product in clinical trials. In light of the extraordinary clinical uncertainties presented, AHIP[1] hereby submits this formal request for a National Coverage Determination (NCD) to clarify whether and under what circumstances Medicare will cover aducanumab.

We understand the heavy toll of Alzheimer's disease on patients, caregivers, and their families and the pressing need for the availability of new FDA-approved treatments that are safe and effective. We believe an NCD is urgently needed to facilitate a consistent national approach to Medicare seniors' access, due to the unique combination of challenges the FDA's approval has created for the Medicare program and the people it serves. The most critical challenges are the limited clinical evidence demonstrating efficacy and the serious safety risks that aducanumab poses for Medicare patients. Further, the prospect for use of aducanumab in a much broader population based on its approved indication versus the more limited population enrolled in clinical trials means that an NCD is necessary to enable the Centers for Medicare & Medicaid Services (CMS) to carefully consider the impact on the Medicare program and the people it serves. This includes more than 26 million seniors and people with disabilities enrolled in Medicare Advantage (MA) and nearly 15 million enrollees in Medicare supplement plans. CMS should also consider the implications of how an NCD may affect future drugs in this class and indicated for the treatment of Alzheimer's disease.[2]

Given these challenges, AHIP's members, many of which offer MA plans and Medicare supplement plans that provide coverage for drugs covered under the Original Medicare program, believe that

[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.

[2] See, e.g., announcement from Eli Lilly that it intends to seek accelerated approval for an Alzheimer's treatment, available at: https://investor.lilly.com/news-releases/news-release-details/lillys-donanemab-receives-us-fdas-breakthrough-therapy

consistent national guidance on the coverage of this treatment and related services is imperative to address the level of access CMS determines is reasonable and necessary for Medicare patients, while ensuring the timely collection of additional evidence. We urge the agency to take swift action in developing this NCD.

Statutorily-defined Benefit Category for Aducanumab

Aducanumab is a medical service, which includes drugs and biologicals which are not usually self-administered by the patient and furnished as an incident to a physician's professional service, that is eligible for coverage under Medicare pursuant to provisions including sections 1832(a)(1) and 1861(s)(2)(A) of the Social Security Act (SSA), to the extent it is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member pursuant to section 1862(a)(1)(A) of the SSA.

Description of Aducanumab and Evidence Supporting Need for NCD Review Process

Per FDA's approved indication labeling,[3] aducanumab is an amyloid beta-directed monoclonal antibody indicated for the treatment of Alzheimer's disease. It was approved based on reduction in amyloid beta plaques observed in patients treated with this product. The label further notes "[c]ontinued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s)." The confirmatory trial(s) are not expected to be completed until 2029, with submission to the FDA in 2030.

FDA approval of this drug under these circumstances and on an accelerated pathway appears to be unprecedented. The FDA's independent expert advisors on the Peripheral and Central Nervous System Drugs Advisory Committee overwhelmingly voted against the recommendation of aducanumab. One of the considerations highlighted by the independent experts on the FDA Advisory Committee was the lack of conclusive evidence presented in the studies. The Institute of Clinical and Economic Review (ICER) also determined that 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.[4] 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." Moreover, aducanumab's efficacy was not demonstrated through a typical clinical endpoint such as a cure or a halting progression of Alzheimer's disease, but rather through a surrogate endpoint of reducing amyloid beta plaque, and, even then, the clinical trials conducted to evaluate aducanumab showed conflicting results.

The publicly-available clinical trial data also 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-edema (ARIA-E), which can be observed on MRI as brain edema or sulcal effusions, and amyloid related imaging abnormalities hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis."[5] Notably, in Studies 1 and 2

[3] https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s000lbl.pdf

[4] See: https://icer.org/wp-content/uploads/2020/10/ICER_ALZ_Revised_Evidence_Report_06302021.pdf

[5] Id. at 4.

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).

In light of the serious safety risks to patients and the conflicting evidence of efficacy, AHIP urges CMS to consider the following questions and recommendations as part of the NCD review process for aducanumab:

1. The FDA's use of an accelerated approval in this situation was based on the conclusion that aducanumab effectively reached the surrogate endpoint of reducing amyloid beta plaque in the trials' populations. The accelerated approval process has typically been used for cancer treatments; use of this approach in this situation may create a precedent for other drugs and devices. Given the limited and conflicting evidence that reductions in amyloid beta plaque benefit patients with Alzheimer's disease, if CMS decides to provide coverage of aducanumab, we urge CMS to consider imposing Coverage with Evidence Development (CED) for this drug, as it will allow for access for patients who would be most likely to potentially benefit while additional clinical evidence is developed. The CED could be helpful in informing the new randomized, controlled clinical trial FDA required the manufacturer to conduct as part of its accelerated approval. Therefore, AHIP believes requiring CED as a condition of coverage is appropriate.

2. If CMS decides to provide coverage of aducanumab, we request that CMS consider under what circumstances, based on the limited clinical evidence, it will consider the treatment medically necessary, and to establish reasonable and necessary criteria that aligns with the population studied in the clinical trial.[6]

3. In clinical trials, amyloid Positron Emission Tomography (PET) scans were used to confirm the presence of amyloid beta plaque prior to enrolling patients in a study for a drug designed to clear the brain of amyloid beta plaque. Aducanumab's mechanism of action and basis for approval is the clearance of amyloid beta plaque. Pursuant to an existing NCD,[7] amyloid PET scans are only covered under CED in clinical studies that meet specified criteria. Consequently, if CMS decides to provide coverage of aducanumab:

    - 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 aducanumab?

    - 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)?

---

[6] Notably, the manufacturer agreed with this approach, stating that: "Based on the entry criteria of the clinical trials conducted with ADUHELM, we estimate the appropriate patient population for ADUHELM to be approximately 1-2 million. These are patients who have been clinically diagnosed with mild cognitive impairment or mild dementia suspected to be due to Alzheimer's disease who would have confirmed amyloid beta pathology, if tested." See: https://investors.biogen.com/news-releases/news-release-details/biogen-and-eisai-update-alzheimers-disease-community

[7] Available at: https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?ncdid=356&ncdver=1&keyword=&keywordType=starts&areaId=all&docType=NCD&contractOption=all&sortBy=relevance&bc=AAAAAAQAAAAA

- 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 aducanumab?

4. Lumbar punctures can also be used to confirm the presence of amyloid beta plaque. If CMS decides to provide coverage of aducanumab, will CMS cover lumbar puncture as an option to diagnose the presence of amyloid beta plaque?

5. The FDA label requires patients to have a magnetic resonance imaging (MRI) scan within the year prior to first being treated with aducanumab and then follow-up MRIs before the seventh and twelfth doses to monitor for brain swelling or bleeding, which was experienced by approximately 40% of patients in the clinical trials. If CMS decides to provide coverage of aducanumab, will CMS require the initial and follow up MRIs as a condition of coverage and to monitor patients for adverse events that were prevalent in the clinical trials (per the FDA label), and, if so, will CMS also reimburse for single/multiple scans as reasonable and necessary?

6. If CMS decides to provide coverage of aducanumab, CMS should provide guidance on the circumstances under which coverage for the treatment is discontinued (e.g., no reduction of amyloid beta plaque, adverse events occur, rapid disease progression, other).

7. CMS should reaffirm guidance that MA plans have the flexibility to determine whether and under what circumstances coverage of aducanumab is reasonable and necessary in the absence of clear CMS guidance for the Original Medicare program, consistent with the provisions of the MA regulations and Chapter 4, section 90.5 of the Medicare Managed Care Manual.

8. We expect that when CMS issues a determination of an NCD it will also acknowledge that aducanumab meets the significant cost criterion in 42 C.F.R. §422.109(a), given the expected financial implications to the Medicare program based on projections of costs and utilization. Thus, Original Medicare, rather than MA plans, would be at risk for providing coverage until the plan year for which the expected costs of aducanumab are reflected in MA benchmarks. We urge CMS to make such a determination at the same time or immediately after an NCD, and to provide clear information on the timeline for such a decision.

The following Appendix includes supporting documentation for this NCD request.

Thank you in advance for your review and consideration of our request. We believe CMS has both an opportunity and a responsibility to ensure there is a national, consistent, and thoughtful set of criteria for coverage of aducanumab and related services, and to provide that guidance as quickly as possible. AHIP welcomes the opportunity to discuss these issues at your convenience.

Sincerely,

Matthew Eyles

Matthew Eyles
President & Chief Executive Officer

Appendix of Supporting Documentation
Request for a National Coverage Determination on Aducanumab

Failure to Demonstrate Efficacy of Aducanumab: An Analysis of the EMERGE and ENGAGE Trials as Reported by Biogen. A systematic review of publicly available data on two phase III clinical trials in mild cognitive impairment and mild dementia due to Alzheimer's disease with the drug aducanumab. Authors conclude that aducanumab's efficacy as a treatment for the cognitive dysfunction in Alzheimer's disease cannot be proven by clinical trials with divergent outcomes. Authors conclude that their analysis supports the conduct of a third, definitive phase III trial.

Peripheral and Central Nervous System Drugs Advisory Committee November 6, 2020 Meeting Transcript. A verbatim transcript from the November 6, 2020, Meeting of the Advisory Committee reflecting the proceedings of the Advisory Committee, including all discussion and vote outcomes pertaining to the biologics license application (BLA) 761178, for aducanumab solution for intravenous infusion, submitted by Biogen Inc., and the Advisory Committee's conclusion that there was insufficient evidence supporting the effectiveness of aducanumab for the treatment of Alzheimer's disease.

Peripheral and Central Nervous System Drugs Advisory Committee November 6, 2020 Final Summary Minutes. Minutes from the November 6, 2020, Meeting of the Advisory Committee summarizing committee discussion and vote outcomes concluding that there was insufficient evidence supporting the effectiveness of aducanumab for the treatment of Alzheimer's disease.

Evaluation of Aducanumab for Alzheimer Disease: Scientific Evidence and Regulatory Review Involving Efficacy, Safety, and Futility. Authors (and members of FDA's Peripheral and Central Nervous System Advisory Committee) reviewed the evidence and literature on aducanumab and concluded that the treatment's earlier conclusion of futility that caused the two phase III trials to be discontinued in 2019 was correct and that post-hoc analyses that change the populations of interest, end points, or methods of analysis, should not overturn this decision.

The American Geriatrics Society Letter to FDA on Aducanumab. Letter to the FDA prior to its approval of aducanumab maintaining that approval of aducanumab at this time is premature based on the lack of sufficient evidence to support that aducanumab reduces progression of Alzheimer's disease and the lack of sufficient evidence to support that the potential benefits as a treatment for patients with mild cognitive impairment (MCI) and Alzheimer's disease could outweigh the potential harms.

ICER Statement on the FDA's Approval of Aducanumab. Statement from ICER highlighting the conclusions of its Draft Evidence Report on Aducanumab that the current evidence is insufficient to demonstrate that aducanumab benefits patients.

FDA Approved Indicating Labeling. Prescribing information for Aduhelm describing the approved indications that go beyond the trial population and the potential adverse reactions, including Amyloid Related Imaging Abnormalities (ARIA).

ICER Evidence Report on Aducanumab. Report from the Institute for Clinical and Economic Review (ICER) that concludes that the clinical trial evidence is insufficient to determine the net health benefit for patients with mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's disease.