February 10, 2022

Administrator Chiquita Brooks-LaSure
Centers for Medicare & Medicaid Services
Department of Health and Human Services
7500 Security Boulevard
Baltimore, MD 21244

RE: NCD Determination for Aduhelm

Dear Administrator Brooks-LaSure:

The Alliance of Community Health Plans (ACHP) applauds the Centers for Medicare & Medicaid Services (CMS) on its balanced decision regarding the proposed National Coverage Determination (NCD) for monoclonal antibodies targeting amyloid for the treatment of Alzheimer's disease. The proposed NCD would include coverage for Aduhelm (Aducanumab), the latest treatment developed for Alzheimer's disease, as well as similar treatments currently under development. The coverage with evidence determination is sound and will allow the opportunity to assess the medical necessity of these types of drugs based upon the collection of additional safety and efficacy data.

As you know, ACHP represents the nation's top-performing, provider-aligned, community-based health plans for more than 24 million Americans nationwide. We support the development and coverage of novel drugs that improve health outcomes, but monoclonal antibodies targeting amyloid have not demonstrated effectiveness, safety or value. We strongly support the agency's goal to ensure that access to this treatment is made based upon strong clinical and scientific evidence that will be gathered through further studies and clinical trials. This proposed coverage decision balances that admirable goal while not giving individuals and families facing the everyday challenges Alzheimer's disease presents a false hope.

ACHP offers this detailed input after consulting with top clinical leaders (such as medical directors and pharmacy leaders) from our member plans. This letter is based on their extensive expertise and understanding based on years of experience in the field. It represents our membership's collective understanding of the available scientific literature and the desire to ensure the best health outcomes for the patients our members are trusted to care for.

Background
Aduhelm was evaluated in two identically designed phase 3 randomized, placebo-controlled clinical trials named Study 301 (ENGAGE) and Study 302 (EMERGE), which had primary objectives to demonstrate efficacy and safety in early Alzheimer's disease.

In 2019, both studies[1] were stopped by Biogen for futility following a planned interim analysis. In 2020, Biogen performed numerous post hoc analyses on the trial data and suggested that in one of the two identical trials

there was a small statistical difference in the rate of cognitive decline as measured by one of the clinical scales used in the trials in the highest dosage arm. Importantly, this difference was not identified in the highest dosage arm of the other identical trial. Additionally, there were no differences in the rate of cognitive decline identified in the lower dosage arms of either trial.

Many scientists and biostatisticians have observed that such a finding during post hoc analysis should be hypothesis-generating and requires confirmation in prospectively designed clinical trials. This is of particular importance since one trial had a positive finding and the other did not. It is not an appropriate assumption to label one of the trials as "true" and the other as "false."

The FDA Advisory Committee charged with reviewing the clinical trial data for Aduhelm all voted against approval due to lack of sufficient evidence of effectiveness on patients. Despite the Advisory Committee's strenuous objections, the FDA ultimately approved[2] Aduhelm under the Accelerated Approval pathway. The agency's decision was based on a reduction in beta-amyloid plaques in the brain. The FDA cited beta-amyloid plaques as a surrogate endpoint, a reduction of which "is reasonably likely to result in clinical benefit."

Since its approval, numerous major health plans – including ACHP member Point32Health – announced they will not cover the drug outside of any national requirement to do so given concerns about the effectiveness and safety of the drug. They are joining a list of major health systems and insurers such as the Cleveland Clinic, Mount Sinai and the Department of Veterans Affairs who are rightfully questioning whether prescribing this treatment is in the best interest of patients.

Lack of Efficacy & Significant Safety Concerns

While Aduhelm has not definitively demonstrated benefit in clinical trials, a significant number of participants in both studies suffered from numerous concerning adverse effects. About 41% of patients in the Phase 3 trials suffered from amyloid related imaging abnormalities (ARIA) including brain swelling (ARIA-E) and small bleeds or microhemorrhages of the brain (ARIA-H). Indeed, one patient treated with Aduhelm in the Phase 1b trial died of an intracranial hemorrhage believed to be related to study treatment.

Of note, the phase 3 clinical trials excluded patients who were on anticoagulant drugs (blood thinners) due to the known risk of ARIA-H (brain bleeds) with Aduhelm. The current FDA label does not list concurrent use of blood thinners as a contraindication, precaution or warning.

There are grave concerns that patients may receive Aduhelm and anticoagulants together with disastrous outcomes, including death from bleeding into the brain. ACHP is encouraged that the Centers for Medicare and Medicaid Services made safety and efficacy a priority in the proposed NCD.

The Concern with Beta-Amyloid Plaques as a Surrogate Endpoint

The full role of beta-amyloid plaques in the pathophysiology of Alzheimer's Disease is not completely understood. While presence of amyloid plaques in patients with cognitive impairment are a hallmark of Alzheimer's disease, their causative role in development of the disease and whether they are an effective therapeutic target remains in doubt.

[1] Alexander GC, *et.al.* Revisiting FDA Approval of Aducanumab. July 28, 2021; DOI: 10.1056/NEJMp2110468
[2] https://www.fda.gov/drugs/news-events-human-drugs/fdas-decision-approve-new-treatment-alzheimers-disease
[3] https://www.cdc.gov/media/releases/2018/p0920-alzheimers-burden-double-2060.html
[4] ICER: Aducanumab for Alzheimer's Disease: Effectiveness and Value. Evidence Report. June 30, 2021.

Additional Resources:
https://www.washingtonpost.com/health/2021/07/05/aduhelm-new-alzheimers-drug-amyloid/
https://www.citizen.org/wp-content/uploads/2575.pdf?eType=EmailBlastContent&eId=76f2ebab-44d9-4b5c-a6a1-2ab30f66c229
https://energycommerce.house.gov/newsroom/press-releases/pallone-and-maloney-commend-cms-s-proposed-medicare-coverage-decision-on
https://www.washingtonpost.com/health/2021/07/09/aduhelm-new-alzheimers-drug-hhs-inspector-general/

Some experts question the validity of using beta-amyloid plaques as a surrogate endpoint to predict likelihood of clinical benefit. This is largely based on the fact that numerous investigational drugs targeting amyloid plaques have failed to demonstrate any improvement in cognitive function decline, despite reducing amyloid plaques.

In addition, it is hypothesized that other markers, including nerve inflammation and tau protein tangles may also play important roles in the disease. Unfortunately, since the controversial FDA approval of Aduhelm was based on beta-amyloid plaque reduction as a surrogate marker, several pharmaceutical companies whose previous anti-amyloid drugs failed to demonstrate any clinical benefit now aim to file for FDA approval of similar drugs. Doubling down on anti-amyloid therapies at this time would likely discourage research for other Alzheimer's treatment targets, which could provide more useful and proven therapeutic modalities in this devastating disease.

As for the randomized controlled trials, there are measures that must be undertaken by Medicare in order to gather wholesome data. Among people ages 65 and older, African Americans have the highest prevalence of Alzheimer's disease and related dementias (13.8 percent), followed by Hispanics (12.2 percent), and non-Hispanic whites (10.3 percent)[4], American Indian and Alaska Natives (9.1 percent), and Asian and Pacific Islanders (8.4 percent). The final coverage with evidence development must ensure that the enrolled patients reflect the nation's diverse population diagnosed with Alzheimer's disease. Patients and families need a clearer understanding of whether a reduction of beta-amyloid plaques provides a clinical benefit that is reflective upon a diverse population and limiting coverage to generate additional evidence is a step in the right direction.

Affordability for the U.S. Healthcare System

There is a well-established prescription drug affordability crisis in the United States, which acutely impacts our nation's public insurance programs and the populations they serve. We applaud the Biden Administration for its continued focus on the problem of exorbitant drugs. Coverage for high-priced, unproven therapeutics will only exasperate existing cost concerns – and do little to improve the health of the nation.

Even with Aduhelm's recently announced price cut, an annual price of $28,200 per patient set by Biogen will have staggering effects on patient access, insurance premiums and taxpayers. The Institute for Clinical and Economic Review's (ICER)[4] panel (which included numerous experts in Alzheimer's disease) unanimously voted against Aduhelm with respect to providing any additional benefits over standard care.

During a cost-effectiveness analysis, ICER's model generously included an assumption that the post hoc analysis finding of delayed cognition decline in the high dose group in the single trial was true. The analysis identified an appropriate value-based annual price range of $3,000 - $8,400, far from the current Aduhelm annual list price and Biogen's staggering $56,000 price at release.

With the aforementioned issues in mind, if Congress acts to allow Medicare to directly negotiate drug prices and those prices cannot be accessed by commercial payers, there will be a massive cost shift to the commercial market, which would undoubtedly result in double digit premium increases for employers and working Americans. In addition, due to the significant safety concerns regarding ARIA-E and ARIA-H, numerous brain

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https://energycommerce.house.gov/newsroom/press-releases/pallone-and-maloney-commend-cms-s-proposed-medicare-coverage-decision-on
https://www.washingtonpost.com/health/2021/07/09/aduhelm-new-alzheimers-drug-hhs-inspector-general/

imaging studies are recommended to monitor for signs of these common adverse effects, which adds to overall costs and patient affordability.

Also, there are concerns that, despite coverage only being available through clinical trials, some costs may be inappropriately pushed onto Medicare. To safeguard the integrity of the trials, CMS should provide guidance to ensure all precisely delineate the conditions under which health care related items and services must be considered as part of the trial, and thus reimbursed by Medicare.

Dr. Lee Fleisher, CMS Chief Medical Officer and Director of the Center for Clinical Standards and Quality noted in the draft decision that due to "the potential for harm, and important questions that remain, we have determined that coverage with evidence development through clinical trials is the right decision for Medicare patients, clinicians, and caregivers." We applaud the proposed national coverage determination for ensuring that the health care system is paying for a drug that is effective and safe.

We appreciate the continued engagement with you and members of your team. ACHP strongly supports this balanced policy, and we encourage CMS to proceed with finalizing the NCD decision for monoclonal antibodies targeting amyloid for the treatment of Alzheimer's disease. Please contact Michael Bagel, ACHP Director of Public Policy, at mbagel@achp.org or (202) 897-6121 with any questions.

Sincerely,

Ceci Connolly
President and CEO
ACHP

Cc: The Honorable Xavier Becerra
Secretary
Department of Health and Human Services

Mr. Paul Spitalnic
Director and Chief Actuary
Office of the Actuary
Centers for Medicare & Medicaid Services

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