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**View Public Comments for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer’s Disease (CAG-00460N)**

Commenter:

Handelman, Justine

Title:

Senior Vice President

Organization:

Blue Cross Blue Shield Association

Date:

08/11/2021

Comment:

August 11, 2021

David Dolan
Centers for Medicare & 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 (CAG-00460N)

Dear Mr. Dolan:

The Blue Cross Blue Shield Association (BCBSA) appreciates the opportunity to provide comments on the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) analysis for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer’s Disease (AD). We understand this analysis includes aducanumab (brand name of Aduhelm) that the Food and Drug Administration (FDA) approved in June 2021 and similar monoclonal antibody treatments for AD that may be approved in the future.

BCBSA is a national federation of 35 independent, community-based and locally operated Blue Cross and Blue Shield companies (Plans) that collectively provide health care coverage for one in three Americans. For more than 90 years, Blue Cross and Blue Shield companies have offered quality health care coverage in all markets across America – serving those who purchase coverage on their own as well as those who obtain coverage through an employer, Medicare and Medicaid.

We share CMS’ commitment to ensuring Medicare coverage of safe and effective treatments for AD, a devastating illness for patients, families and caregivers. We also recognize that there is no cure for AD and that treatment options are critical for this debilitating brain disorder. However, for reasons detailed below, we feel strongly that aducanumab does not meet the statutory coverage standard of “reasonable and necessary” as the current evidence highlights numerous safety risks and uncertain clinical benefits.

The FDA approval of aducanumab has generated interest from the hundreds of thousands of patients who may be eligible for this treatment. Patients, their families and treating physicians deserve an evidence-based analysis of current, reliable clinical data on aducanumab, as well as a thoughtful federal approach as the sponsor continues evidence generation in the next clinical trials. We commend CMS for its careful analysis of the peer-reviewed and published clinical evidence, benefits and serious profile of side effects for this therapy class of Monoclonal Antibodies Directed Against Amyloid for the Treatment of AD.

As CMS conducts this analysis, we recommend strict application of the “reasonable and necessary” framework to determine aducanumab’s safety and effectiveness. By doing so, CMS will be able to assess if aducanumab lacks sufficient data for coverage and deems the product experimental/investigational, or, if the outstanding efficacy questions and the limitations in peer-reviewed published literature suggests coverage with evidence development. CMS should incorporate the FDA Advisory committee’s conclusions and other expert opinion on the efficacy and safety of aducanumab as it assesses if the product satisfies the “reasonable and necessary” standard.

We also encourage CMS to consider the long-term impact of the potential approval for this drug, and whether it could undermine the “reasonable and necessary” Medicare coverage standard, which can have ramifications for future opportunities to develop effective treatments and for patient safety. We are concerned that the premature FDA approval of this drug with inconclusive evidence could lower the safety and efficacy standards for future drug approvals.

However, if CMS does decide to cover aducanumab, it is critical that it be covered under “coverage with evidence development” and should target the appropriate patient population based on clinical trials. This approach would offer access to targeted populations while collecting much-needed data for all interested parties about the drug’s effectiveness and safety long before the FDA’s required post-approval studies are completed.

What is most important in the NCD analysis is to focus on the science and the well-being of patients. We provide the following key considerations:

* Support objective health outcomes that are meaningful to patients and their families, including maintaining independence and activities of daily life.
* Acknowledge the conclusion of FDA statistical review, which found “no compelling correlation between effects on amyloid beta plaques and effects” on progression of dementia.
* Assess the benefit-risk ratio for patients considering aducanumab treatment, with a special focus on amyloid-related imaging abnormalities (ARIA), whose clinical effects can range from asymptomatic to severe.
* Urge the design of the NCD to support completion of the confirmatory trial as soon as possible to confirm whether there is clinical benefit.
* Recommend an independent authoritative review of all relevant evidence that reduction in beta amyloid is a surrogate for mitigation of cognitive decline in AD, since the relationship between clearance of beta-amyloid in the brain and clinical improvement has yet to be conclusively demonstrated.

We appreciate your consideration of our recommendations. We look forward to continuing to engage with CMS as the agency progresses on the NCD analysis and considers other key actions.

Sincerely,

Justine Handelman, Senior Vice President, Office of Policy and Representation
John A. Fallon, MD, Interim Chief Medical Officer, Office of Clinical Affairs

BCBSA DETAILED COMMENTS ON CMS’ NATIONAL COVERAGE DETERMINATION FOR MONOCLONAL ANTIBODY TREATMENTS FOR ALZHEIMER’S DISEASE

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

Response

BCBSA supports recognizing health outcomes that have a measured impact on cognition and function as identifiers that a treatment delays progression of AD. We also recommend CMS understand the outcome measures that would guide discontinuation of therapy as well.

We emphasize the following for assessing health outcomes:

* Systematically studying the preservation of independence and maintaining activities of daily life and quality of life.
* Use of a battery of cognitive tests versus a single test to identify individuals with mild cognitive impairment due to AD or mild dementia due to AD. The tests should evaluate multiple domains such as cognition (memory, orientation, judgment/problem solving) and function (community affairs, home and hobbies and personal care); although specific tests may vary. o Screening tests, such as Mini-Mental State Exam (MMSE) and the Montreal Cognitive Assessment Test for Dementia (MoCA), although used commonly in clinical practice are not sufficient for diagnosis.
* Collection of outcome measures should be conducted in a manner that minimizes the burden on patients and family or caregivers.
* The follow-up period to collect outcome data should be at least 2 years and preferably longer. In the pivotal trials, treatment effect was observed at 78 weeks in the EMERGE trial. Therefore, longer follow-up is more likely to capture any treatment effect.

Should CMS explore a coverage with evidence development (CED) as a part of the NCD, we believe that the key questions for CED framework should be:

* Does aducanumab slow cognitive and functional impairment in early AD?
* What is the benefit-risk ratio for use of aducanumab?
* Is there a threshold for reduction in brain amyloid levels that is associated with clinical benefit in the mitigation of progression of AD?
* Is there a threshold for progression of AD that indicates no further clinical benefit can be expected from aducanumab?

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

Response:

We urge CMS to rely on the criteria used in the pivotal trial and the FDA label in examining those characteristics of patients who may see a positive outcome while mitigating adverse events for patients who are at higher risk. Based on this standard, the following criteria may identify the population that may benefit with treatment with aducanumab:

* Individuals with a positive amyloid-beta (Aß) Positron emission tomography (PET) scan and
* Mild cognitive impairment due to AD, or mild dementia due to AD

The following individuals may not benefit or may be at an increased safety risk with treatment with aducanumab based on the clinical trials:

* Advanced stages of dementia
* Serious comorbidities
* Other advanced neurodegenerative disease
* Use of antiplatelet or anticoagulant therapy (other than aspirin at =325 mg daily)

When patients and treating physicians are discussing aducanumab as an AD treatment option, it is important to: discuss risk benefit ratio; gauge the patients’ ability to follow the treatment and imaging regimens; and address logistical support for scheduling, transportation and follow-up. Treating physicians and patients need to discuss and acknowledge the potential safety risks, including ARIA. Patients also need a support system for reporting adverse signs and symptoms of ARIA and a safe home environment (e.g., risk prevention strategies). These conditions should be met to increase the likelihood of patients completing the treatment regimen, regularly measuring the effectiveness of the treatment, and mitigating safety risks for patients.

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

Response:

As the health insurance providers to more than 111 million Americans, BCBSA believes everyone should have access to high-quality health care regardless of race, ethnicity, national origin, sex, gender identity, sexual orientation or age. This extends to equitable patient access for the diagnosis and treatment of AD.

Evidence available from clinical trials of aducanumab is not representative of the patient demographics of AD in the US. We therefore recommend CMS require better representation of minority groups in future evidence generation.

CMS may wish to engage with the Office of Minority Health in an equity assessment as part of this NCD analysis. Using these tools requires a commitment to operating in a different way and, while they can sometimes be laborious, experience has shown them to be effective in targeting policy solutions to meet the needs of communities experiencing the greatest inequities and disparities. Blue Cross Blue Shield Plans have found that the most effective assessment processes include a strong focus on community engagement. The localities that have prioritized community engagement are also the ones that have experienced the most impactful equity work. An equity assessment tool for the delivery of aducanumab will gauge the levels of access for different patient populations.

We offer the following considerations in addressing issues of equity and inclusion in access to treatment of AD. Concerns include whether there is access to:

* Care in a specialized center
* Family or caregiver support for managing the disease
* Family or caregiver education and respite care
* Logistical support for scheduling, transportation and follow-up
* Community support, broadband access/patient portal use
* Having a culturally diverse interdisciplinary team that matches the local community it serves

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?

Response:

BCBSA supports an interdisciplinary health care delivery teams that includes:

* Psychometricians, neuropsychiatrists, neurologists and/or geriatricians experienced in diagnosing, treatment and management of AD
* Trained and experienced radiologists to interpret amyloid PET scans
* Trained and experienced radiologists to interpret MRI for interpretation of baseline superficial siderosis and micro hemorrhages and subsequent sequential imaging for clinical vigilance for ARIA and grading severity of ARIA
* Patient navigators to help guide the patient and family through the care delivery system.
* Pharmacists – It is likely these patients may have other co-morbid conditions and would be important to have a perspective on how aducanumab may or may not be affecting other therapies for appropriate education and counseling.

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

Response:

BCBSA believes treatment with aducanumab should be delivered in AD Research Centers or in such centers paired with community practices. Pairing specialized centers with community practices has been demonstrated to be effective in cancer care. We suggest testing the feasibility of a hub and spoke model, which is known to improve the quality of complex care delivered in community settings, to provide access to communities where specialized facilities are unavailable. This model would improve the equity of access to treatment for patients who do not live near one of these specialized centers. Should CMS cover aducanumab, patients should also have the option of receiving the drug through home infusion with appropriate patient support.

Additional Comments

BCBSA also recommends the following as part of the NCD process:

* Convene an expert panel at the National Academy of Medicine to provide a comprehensive assessment of the current evidence that a decline in beta amyloid is a surrogate for mitigation of cognitive decline in AD; and
* Review and address key questions related to Medicare’s coverage of PET scans.

As a part of the NCD analysis and for future understanding of AD, we urge that a National Academy of Medicine Expert Panel be created and charged with a thorough examination and analysis of existing evidence that reduction in beta amyloid is a surrogate for mitigation of cognitive decline in AD. While a complete analysis may take 18 months to two years to complete, the panel could be charged with delivering an interim report appropriate with the NCD development timeline.

A significant portion of the AD pharmaceutical development is focused on beta amyloid plaque reduction. The overall objective is for an expert panel to produce an independent, rigorous, and thorough review of the potential of amyloid beta plaque reduction for use as a surrogate outcome for mitigation of cognitive decline in AD. BCBSA recommends the follow conditions for this panel:

* All potentially relevant sources should be reviewed, including: prior efforts to target amyloid and associated failures; data from aducanumab pivotal trials and earlier studies; and data from other amyloid targeting drugs currently in clinical trials and preclinical studies.
* Clinical trial sponsors should contribute patient level data.
* Key variables for stratifying data should be developed and applied in various analyses and sensitivity analysis. Some potential variables of interest include approach to drug targets, pathways of action, dosage and dose limitations.

For the type of report we recommend, one precedent is the 2015 National Academies’ (then Institute of Medicine) report “Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness.”

Additionally, there are significant data limitations and issues with the two Phase III clinical trials, which makes is difficult to draw meaningful conclusions about efficacy. The results of these studies should be interpreted with caution due to the lack of clinical benefit demonstrated in the pre-specified primary analysis and the conflicting results between the two studies. Below are the limitations and challenges in the two Phase III clinical trials, which should be addressed in future clinical trials:

* Lack of published Phase III clinical trials for aducanumab.
* No replication of data from clinical studies. The two Phase III trials revealed highly conflicting results, as well as, conflicting subgroup results.
* Only 53% and 54% of individuals in the ENGAGE and EMERGE trials, respectively, were included in the intention-to-treat analysis.
* The higher corresponding dropout rates (47% in ENGAGE and 46% in EMERGE) do not meet the preplanned 30% assumed dropout rate which would allow for detecting a true difference between aducanumab and placebo.
* Only 27.8% of individuals in EMERGE and 24.5% of individuals in ENGAGE completed a full 14 weeks of high-dose (10 mg/kg) treatment.
* Loss of randomization contributes to bias.
* In the ENGAGE trial, no statistically significant differences were observed between the aducanumab-treated and placebo-treated individuals in the primary efficacy endpoint.
* Data from a smaller subgroup of individuals in the EMERGE trial indicated a reduced clinical decline. The difference compared to placebo in CDR-SB was 0.39 on an 18-point scale, however, a change of at least 1 is considered clinically significant.

Finally, we recommend CMS consider and address the following questions given the importance of diagnosing patients with PET scans to determine treatment eligibility:

* 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)?
* Based on Medicare’s ongoing CED requirement for use of PET imaging, will fee-for-service 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?
* Will Cerebrospinal Fluid (CSF) testing for amyloid beta be covered as an alternative to the amyloid PET?
* Should CMS decide to cover PET scans, we recommend that separate consideration is given to the following scenarios:
	+ One time use to establish the diagnosis of AD;
	+ Diagnosis for other indications;
	+ Management of patients on aducanumab to assess therapy response; and
	+ Screening asymptomatic patients at risk for AD.