Medical Drug Clinical Criteria

Subject:	Aduhelm (aducanumab)		
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Overview

This document addresses the use of Aduhelm (aducanumab-avwa)**.** Aduhelm is a human monoclonal IgG1 anti-amyloid beta antibody indicated for the treatment of Alzheimer's disease (AD).

Upon approval, Aduhelm was broadly indicated for the treatment of Alzheimer's disease (Aduhelm Label, June 2021). The label was amended one month after approval to indicate the following (Aduhelm Label, July 2021):

Treatment with Aduhelm 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 in initiating treatment at earlier or later stages of the disease than were studied.

Aduhelm was FDA-approved under accelerated approval based on reduction in amyloid beta plaques observed in individuals treated with Aduhelm (Aduhelm Label 2021). Although an association between abnormal amyloid beta accumulation and cognitive decline has been reported (Aduhelm Label 2021), it is uncertain whether amyloid beta plaque reduction results in clinically meaningful benefit. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s) (Aduhelm Label 2021). The manufacturer has up to 9 years to submit results from a confirmatory clinical trial. Currently, there is no direct evidence that Aduhelm results in clinical benefit for individuals with Alzheimer's disease based on no replication of data from trials, highly conflicting results from two studies, and conflicting subgroup results (FDA Peripheral and Central Nervous System Drugs Advisory Committee, November 2020).

Aduhelm was studied in two 18-month, randomized, double-blind, placebo-controlled global phase 3 trials – EMERGE (Study 302; NCT02484547; Haeberlein 2022) and ENGAGE (Study 301; NCT02477800; Haeberlein 2022) – with identical design that evaluated safety and efficacy in individuals aged 50-85 with early Alzheimer's disease (mild cognitive impairment due to AD or mild AD dementia) and presence of amyloid beta. The phase 3 trials were randomized 1:1:1 to low-dose Aduhelm (6 mg/kg), high-dose Aduhelm (10 mg/kg) or placebo administered via IV infusion every 4 weeks. The prespecified primary endpoint for both studies was change in the Clinical Dementia Rating – Sum of Boxes (CDR-SB) from baseline to 78 weeks. For both studies there was a mid-study protocol amendment to increase the target dose for ApoE ε4 carriers from 6 mg/kg to 10 mg/kg. Both phase 3 studies were terminated early based on a planned futility analysis that concluded the primary endpoint would not be met. Following termination, a post-hoc subgroup analysis that included additional participants during a 3-month open label period was conducted.

Only 53% and 54% of individuals in the ENGAGE and EMERGE trials, respectively, were included in the intention-to-treat analysis. The corresponding dropout rates (47% and 46%, respectively) do not meet the preplanned 30% assumed dropout rate which would allow for detecting a true difference between Aduhelm 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 (Knopman 2021). Loss of randomization also contributes to bias. Bias could arise when there are flaws in the design and management of a trial. In the ENGAGE trial, no statistically significant differences were observed between the Aduhelm-treated and placebo-treated individuals in the primary efficacy endpoint. Data from a subset 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 (change of at least 1 is considered clinically significant [Andrews 2019]). Results of these studies should be interpreted with caution due to lack of clinical benefit demonstrated in the prespecified primary analysis and the conflicting results between the two studies (FDA Peripheral and Central Nervous System Drugs Advisory Committee Meeting, November 2020). There is uncertain correlation between changes in the primary biomarker, amyloid beta, and improvement in cognitive function or reduction in decline of cognitive function. There is no sufficiently reliable evidence that any observed treatment effect on biomarker measures would be reasonably likely to predict clinical benefit (the standard for accelerated approval), despite a great deal of research interest in understanding the role of biomarkers in AD (FDA Draft Guidance, 2018). Reduction in amyloid beta, measured through standard uptake value ratio (SUVR) on Positron Emission Tomography (PET) scan, was considered a pharmacodynamic endpoint in Aduhelm trials. In EMERGE, only 33% of patients were evaluated for amyloid beta reduction and only 18% had week 78 data (FDA

Statistical Review, June 2021). In ENGAGE, only 36% of patients were evaluated for amyloid beta reduction and 21% had week 78 data (FDA Statistical Review, June 2021). The FDA statistical review states there is no evidence that amyloid change based on SUVR is a surrogate marker for clinical change; and that these data should be considered exploratory (FDA Statistical Review, June 2021).

There are safety concerns with Aduhelm as use increases the risk of amyloid-related imaging abnormalities (ARIA). ARIA can be observed on magnetic resonance imaging (MRI) as brain edema or sulcal effusions (ARIA-E) or microhemorrhage and superficial siderosis (ARIA-H). In clinical studies, ARIA was observed in over 40% of individuals taking high dose Aduhelm compared with 10% of individuals taking placebo. In study 302 (EMERGE), 34% of patients presented with ARIA-E (edema) and 33.5% of patients presented with ARIA-H (hemosiderin deposition) that included microhemorrhage (19.7%), superficial siderosis (13.3%) and cerebral hemorrhage (0.5%). The long-term effect of ARIA in individuals with dementia is unknown. The majority of ARIA-E radiographic events occurred early in treatment (within the first 8 doses), although ARIA can occur at any time. It is unclear if the risk of ARIA observed in the EMERGE and ENGAGE trial are representative of risks of ARIA anticipated in a real-world setting.

Frequency of ARIA in the placebo-controlled period of EMERGE (Study 302) (FDA Advisory Committee Presentation, November 2020)

Term	Aducanumab 10 mg/kg N = 547 %	Placebo N = 548 %
Subjects with ARIA events	41.7	10.2
Subjects with symptomatic ARIA	7.5	0.4
ARIA-E	34.4	2.4
ARIA-H (microhemorrhage)	19.7	6.8
ARIA-H (superficial siderosis)	13.3	2.6
ARIA-H (cerebral hemorrhage)	0.5	0.0

The label offers dosing recommendations for patients who experience ARIA, but suggests that the clinician should use clinical judgement when deciding if Aduhelm should be continued or permanently discontinued once MRI shows stabilization and symptoms resolves. However, there is no clear data on continued dosing following detection of radiographically moderate or severe ARIA. In the Phase 3 studies EMERGE and ENGAGE, temporary dose suspension was required for radiographically moderate or severe ARIA-E and radiographically moderate ARIA-H. In studies, permanent discontinuation of dosing was required for radiographically severe ARIA-H (Aduhelm Label 2021, Warnings and Precautions) defined as 10 or more new incident microhemorrhages or greater than 2 focal areas of superficial siderosis. Additionally, label update on 4/29/22 also added risk of seizures to Warnings and Precautions, including status epilepticus, associated with ARIA that was reported in the placebo-controlled and long-term extension studies for Aduhelm.

In 2020, the FDA Peripheral and Central Nervous System Drugs Advisory Committee, an independent group of individuals, determined there was not strong evidence to support FDA approval of aducanumab. The committee vote was 10 votes against FDA approval for aducanumab and 1 vote uncertain for approval of aducanumab. This was based on the conflicting studies and unclear benefit. The Advisory Committee was not presented the possibility of accelerated approval based on the biomarker of reduction in amyloid beta plaques (FDA Peripheral and Central Nervous System Drugs Advisory Committee Meeting, November 2020).

Based on the currently available evidence, there is no valid scientific data to show that the expected health benefits from Aduhelm are clinically significant and will have a greater chance of benefit, without a disproportionately greater risk of harm or complications.

The American Academy of Neurology (AAN) issued a report in April 2022 on the use of Aduhelm, and stated that whether aducanumab will result in a clinically meaningful slowing of AD symptoms remains to be determined, as does the safety of aducanumab in clinical populations. AAN emphasized that future research is needed to determine whether aducanumab-related reductions in cerebral amyloid burden translate to clinically meaningful outcomes. In the absence of high-quality data to inform these questions, uncertainty surrounding the optimal use of aducanumab in clinical practice will remain.

On April 7, 2022, the Centers for Medicare & Medicaid Services (CMS) released a National Coverage Determination (NCD) for Aduhelm which stated that it would only be considered under *coverage with evidence development (CED)* when the specified criteria outlined within the NCD are met. Aduhelm NCD includes a requirement that use must be within the confines of a FDA approved randomized controlled trial, CMS approved studies, or other studies supported by the NIH.

Aduhelm has been discontinued by the manufacturer. Criteria will remain active until the drug is no longer active in drug files as claims can adjudicate several years after agent discontinuation.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Aduhelm (aducanumab)

Requests for Aduhelm (aducanumab) for any diagnosis may not be approved.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J0172	Injection, aducanumab-avwa, 2 mg Aduhelm

ICD-10 Diagnosis

All diagnoses pend

Document History

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- 08/16/2024 – Annual Review: No changes. Coding Reviewed: No changes.
- 08/18/2023 – Annual Review: No changes. Coding Reviewed: No changes.
- 08/19/2022 – Annual Review: No changes. Coding Reviewed: No changes.
- 04/19/2022 – Select Review: Add new clinical criteria document for Aduhelm. Coding Reviewed: Added HCPCS J0172. All diagnoses pend.

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Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.