Effective Date **9/15/2021**
Next Review Date… **9/15/2022**
Coverage Policy Number **IP0200**

Aducanumab

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Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy addresses the usage of Aducanumab (Aduhelm™).

Medical Necessity Criteria

Aducanumab (Aduhelm) for the treatment of Alzheimer's disease is considered experimental, investigational, or unproven.

> **Note:** *Aduhelm is FDA-approved for the treatment of Alzheimer's disease in adults; however, there is insufficient clinical efficacy data supporting this use.*

Conditions Not Covered

Aducanumab (Aduhelm) is considered experimental, investigational or unproven for **ANY** use, including the following (this list may not be all inclusive):

1. **Alzheimer's disease, mild cognitive impairment or dementia stage of disease.** Due to insufficient clinical efficacy data, approval is not recommended for Aduhelm.
    - In a Phase Ib study, patients were enrolled with a global CDR score of 0.5 or 1.0. Approximately halfway through the two Phase III studies, a planned interim analysis met prespecified futility criteria and the trials were terminated prior to completion. A post-hoc analysis of the trials revealed that EMERGE did reach statistical significance on its primary efficacy endpoint, estimating a high-dose treatment effect corresponding to a 22% relative reduction in the Clinical Dementia Rating–Sum of Boxes (CDR-SB) score compared with placebo (P = 0.01). Efficacy was not demonstrated in the low-dose arm of EMERGE or in either treatment arm of ENGAGE. Of note, the minimum clinically important difference for the primary endpoint of CDR-SB is generally considered to be 1 to 2 on a scale from 0 to 18. The 22% reduction in CDR-SB detected in the high-dose arm in EMERGE reflected an absolute difference of 0.39, which does not qualify as clinically significant.

2. **Alzheimer's disease, moderate or severe cognitive impairment or dementia stage of disease.** There are no safety or effectiveness data on initiating treatment at later stages of the disease than were studied.[1]

Coding / Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Experimental/Investigational/Unproven:

HCPCS Codes	Description
J0172	Injection, aducanumab-avwa, 2 mg (Code effective 01/01/2022)

Background

OVERVIEW
Aduhelm, an amyloid beta-directed antibody, is indicated for the treatment of Alzheimer's disease in patients with mild cognitive impairment or mild dementia stage of disease.[1]

This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with Aduhelm.[1] Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

Disease Overview
An estimated 6.2 million Americans ≥ 65 years of age are living with Alzheimer's dementia in 2021, with 72% of these people ≥ 75 years of age. The number and proportion of older adults who have mild cognitive impairment due to Alzheimer's disease is difficult to estimate; however, a rough approximation is approximately 5 million older Americans may have mild cognitive impairment due to Alzheimer's disease. People with mild cognitive impairment due to Alzheimer's disease have biomarker evidence of brain changes due to the disease in addition to subtle problems with memory and thinking. Biomarker evidence includes abnormal levels of amyloid beta as evidenced on positron emission tomography (PET) scans and in analysis of cerebrospinal fluid (CSF), and decreased metabolism of glucose as shown on PET scans. These cognitive problems may be noticeable to the individual family members and friends, but not to others, and they do not interfere with the person's ability to carry out everyday activities. The mild changes in cognitive abilities occur when the brain can no longer compensate for the damage and death of nerve cells due to Alzheimer's disease. Among those with mild cognitive impairment, about 15% develop dementia after 2 years. Approximately 32% of people with mild cognitive impairment develop Alzheimer's dementia within 5 years.

Clinical Efficacy
To determine the clinical efficacy of Aduhelm, two nearly identical, Phase III, double-blind, placebo-controlled, randomized trials of high- and low-dose Aduhelm (ENGAGE and EMERGE) were conducted in patients with Alzheimer's disease (patients with confirmed presence of amyloid pathology and mild cognitive impairment or mild dementia stage of disease).[1] Patient enrollment criteria included the following for the two pivotal studies: Clinical Dementia Rating (CDR) global score of 0.5 and a Mini-Mental State Examination (MMSE) score of 24-30. In a Phase Ib study, patients were enrolled with a global CDR score of 0.5 or 1.0. Approximately halfway through the two Phase III studies, a planned interim analysis met prespecified futility criteria and the trials were terminated prior to completion. A post-hoc analysis of the trials revealed that EMERGE did reach statistical significance on its primary efficacy endpoint, estimating a high-dose treatment effect corresponding to a 22% relative reduction in the Clinical Dementia Rating–Sum of Boxes (CDR-SB) score compared with placebo (P = 0.01). Efficacy was not demonstrated in the low-dose arm of EMERGE or in either treatment arm of ENGAGE. Of note, the minimum clinically important difference for the primary endpoint of CDR-SB is generally considered to be 1 to 2 on a scale from 0 to 18. The 22% reduction in CDR-SB detected in the high-dose arm in EMERGE reflected an absolute difference of 0.39, which does not qualify as clinically significant.

Dosing Information
Aduhelm is titrated up to the recommended dose of 10 mg/kg over 6 months. Aduhelm is given every 4 weeks as an intravenous (IV) infusion given over 1 hour. Dosing of Aduhelm is initiated at 1 mg/kg for infusions one and two, then 3 mg/kg for infusions three and four, then 6 mg/kg for infusions five and six, and 10 mg/kg for infusion seven and beyond. Aduhelm has not demonstrated efficacy when titrated to a maximum dose 3 or 6 mg/kg. Doses of 10 mg/kg were required in order to show effectiveness.

Safety
Aduhelm can cause amyloid related imaging abnormalities-edema (ARIA-E) and amyloid related imaging abnormalities-hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis, which can be observed on magnetic resonance imaging (MRI).[1] A recent (within 1 year) MRI of the brain should be obtained prior to initiating treatment with Aduhelm. The safety of Aduhelm in patients with any pre-treatment localized superficial siderosis, ten or more brain microhemorrhages, and/or with a brain hemorrhage > 1 cm within one year of treatment initiation has not been established. Enhanced clinical vigilance for ARIA is recommended during the first eight doses of treatment with Aduhelm, particularly during titration, because the majority of ARIA was observed during this time. MRIs of the brain should be obtained prior to the 7th infusion (first dose of 10 mg/kg) and 12th infusion (sixth dose of 10 mg/kg) of Aduhelm to evaluate for the presence of asymptomatic ARIA. If ten or more new incident microhemorrhages or greater than two focal areas of superficial siderosis (radiographic severe ARIA-H) are observed, treatment may be continued with caution only after a clinical evaluation and a follow-up MRI demonstrates radiographic stabilization (i.e., no increase in size or number of ARIA-H).

Guidelines
Aduhelm is not addressed in guidelines. The American Academy of Neurology (AAN) published a guideline on mild cognitive impairment in 2018, prior to the approval of Aduhelm.[20] The appropriate diagnosis of mild cognitive impairment is important in order to assess for reversible causes of cognitive impairment, to help patients and families understand the cause of their cognitive concerns, and to discuss likely outcomes, allowing the patient and family to plan appropriately. However, sharing the diagnosis must be balanced with the potential harm of anxieties from diagnosing a patient with a condition that may not progress. If the patient or a close contact voices concern about memory or impaired cognition, clinicians should assess for mild cognitive impairment with validated tools and not assume the concerns are related to normal aging (Level B). Some cases of mild cognitive impairment are associated with reversible causes, including medication AEs, sleep apnea, depression, and other medical conditions; patients should undergo a medical evaluation for risk factors that may be treatable (Level B). Cognitively impairing medications should be discontinued where possible and behavioral symptoms treated (Level B). Patients and families should be informed that no pharmacologic or dietary agents have currently demonstrated symptomatic cognitive benefit in mild cognitive impairment and no medications are FDA-approved for this purpose (Level B). Studies of cholinesterase inhibitors (ChIs) showed no benefit on cognitive outcomes or reduction in progression from mild cognitive impairment to dementia, although some studies could not exclude an important effect. Also, AEs with cholinesterase inhibitors are common, including gastrointestinal symptoms and cardiac concerns. Clinicians may choose not to offer (Level B), and if the decision is made to

prescribe a ChI, the lack of evidence must be discussed (Level A). Regular physical exercise should be offered as part of an overall approach (Level B) and cognitive training may be recommended based on the potential for improved cognitive function (Level C).

The AAN posted an "Aducanumab Resources" page on their website to assist in understanding the current landscape with the availability of Aduhelm and to provide discussion points for practitioners' use with patients.[21] In July 2020, AAN formed a work group of experts in health policy, science, and education to prepare for the potential release of Aduhelm and its implications for neurologists and their patients. The Academy is developing an Evidence in Focus document to summarize the level of evidence for patients with Alzheimer's disease and review clinical considerations regarding use. This is not a guideline and does not include recommendation statements. This is a narrowed assessment of evidence that is developed more quickly than a traditional guideline.

References

1. Aduhelm™ injection for intravenous use [prescribing information]. Cambridge, MA: Biogen; June 2021.
2. Biogen pre-approval dossier.
3. Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee Meeting. Combined FDA and Applicant PCNS Drugs Advisory Committee Briefing Document. November 6, 202.
4. Alzheimer's Association. Alzheimer's disease facts and figures-2021. Available at: https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf. Assessed on June 7, 2021.
5. Alexander GC, Emerson S, Kesselhelm AS. Evaluation of aducanumab for Alzheimer Disease scientific evidence and regulatory review involving efficacy, safety, and futility. *JAMA*. Published online March 30, 2021.