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Aducanumab

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Overview

This policy addresses the usage of aducanumab (**Aduhelm**[®]).

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.** The current Aduhelm efficacy information is insufficient to determine if the medication demonstrates any clinically meaningful benefits. In the absence of additional clinical trials, there is not enough information to support approval.
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

Background

OVERVIEW

Aduhelm, an amyloid beta-directed antibody, is indicated for the **treatment of Alzheimer's 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 6.7 million Americans \geq 65 years of age are living with Alzheimer's dementia in 2023, with 73% of these people \geq 75 years of age.² 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 suggests that 5 to 7 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, 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.

Clinical Efficacy

The current Aduhelm efficacy information is insufficient to determine if the medication demonstrates any clinically meaningful benefits. In the absence of additional clinical trials, there is not enough information to support approval.

Alzheimer's Disease. Due to the lack of clinical efficacy data, approval is not recommended for Aduhelm. The prescribing information for Aduhelm states that it was approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with Aduhelm.¹ FDA has required a randomized, controlled trial evaluation post-marketing to establish efficacy of Aduhelm. Results are expected in 2030.

Two 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).^{1,3,4} 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 18.⁵ 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.

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 asymptomatic amyloid related imaging abnormalities (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 seventh 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 demonstrate radiographic stabilization (i.e., no increase in size or number of ARIA-H).

References

1. Aduhelm™ intravenous infusion [prescribing information]. Cambridge, MA: Biogen; February 2023.
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3. Budd Haeberlein S, Aisen PS, Barkhof F, et al. Two randomized phase 3 studies of aducanumab in early Alzheimer's Disease. *J Prev Alzheimers Dis.* 2022;2(9):197-210.
4. Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee Meeting. Combined FDA and Applicant PCNS Drugs Advisory Committee Briefing Document. November 6, 2020. Available at: <https://www.fda.gov/media/143502/download>. Accessed on June 2, 2023.
5. Alexander GC, Emerson S, Kesselhelm AS. Evaluation of aducanumab for Alzheimer Disease scientific evidence and regulatory review involving efficacy, safety, and futility. *JAMA.* 2021;325(17):1717-1718.

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