

Aduhelm™ (aducanumab-avwa)

Document Number: OHSU HEALTHSERVICES

Date of Origin: 06/23/2021

Last Review Date: 07/28/2021

Effective Date: 07/28/2021

Dates Reviewed: 06/23/2021, 07/28/2021

Developed By: Medical Criteria Committee

I. Length of Authorization

- A. Authorization is valid for 12 months and may be renewed.

II. Dosing Limits

- A. Max Units [HCPCS Unit]:
 - i. **Alzheimer's Disease**
 - 1. Initial: 1,600 mg for 6 months
 - 2. Renewal: 4,800 mg for 6 months

III. Initial Approval Criteria

- A. **Alzheimer's Disease**
 - i. Patient is ineligible for Alzheimer's disease clinical trial enrollment for aducanumab (Aduhelm) or other investigational therapies; **AND**
 - ii. The medication is prescribed by, or in consultation with, a specialist in neurology or gerontology; **AND**
 - iii. Patient is 50 years of age or older; **AND**
 - iv. Patient does not have a bleeding disorder, brain hemorrhage, cerebrovascular abnormalities, or is being treated with blood thinners (except aspirin at a prophylactic doses); **AND**
 - v. Confirmation of ongoing monitoring of Amyloid-Related Imaging Abnormalities (ARIA); **AND**

- vi. Patient is diagnosed with Mild Cognitive Impairment (MCI) due to Alzheimer’s disease OR mild Alzheimer’s disease when ALL of the following are met:
 1. Documented cognitive decline of at least six months reported by family, caregivers, and/or provider; **AND**
 2. Objective evidence of cognitive impairment at baseline as defined by the following:
 - i. Clinical Dementia Rating (CDR) Global Score of 0.5; **AND**
 - ii. Mini Mental State Exam (MMSE) score of 24 or higher; **AND**
 - iii. Repeatable Battery for Assessment of Neuropsychological Status (RBANS) score of 85 or below; **AND**
 3. Imaging techniques (Magnetic Resonance Imaging [MRI], Computerized Tomography [CT] scan) have been utilized to exclude other causes of cognitive impairment (e.g., brain tumor, stroke); **AND**
 4. Other etiologies of cognitive impairment have been excluded (e.g., alcohol or substance abuse, psychiatric illness, medications); **AND**
 5. A biomarker associated with AD is present (amyloid PET, tau PET, CSF β -amyloid)

IV. Renewal Criteria

- A. Patient has responded to therapy compared to pretreatment baseline as evidenced by improvement, stability, or slowing in cognitive and/or functional impairment in one or more of the following: MMSE, CDR, RBANS, ADAS-Cog13, ADCS-ADL-MCI, MMSE, CDR-SB; **OR**
- B. Repeat PET scan demonstrates reduction in amyloid compared to baseline; **AND**
- C. Patient has not progressed to moderate or severe Alzheimer’s disease; **AND**
- D. Confirmation of ongoing monitoring and management of Amyloid-Related Imaging Abnormalities (ARIA)

V. Supporting Evidence

- A. Aducanumab (Aduhelm) is indicated for the treatment of Alzheimer disease in patients with mild cognitive impairment or mild dementia stage of disease. It is a monoclonal antibody that targets the buildup of amyloid plaque in the brain and is administered once monthly as an intravenous infusion.
- B. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with aducanumab (Aduhelm). Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.
- C. In November 2020 an independent panel of experts advising the FDA evaluated the data and argued that the benefit of aducanumab (Aduhelm) did not outweigh the risks. Ten of the eleven panelists voted that the presented data could not be considered as evidence of effectiveness, while the remaining panelist was uncertain. Although the FDA does not have to take the recommendation of the Advisory Committee, it generally does.
- D. Originally the FDA broadly approved the use of aducanumab (Aduhelm) for “the treatment of Alzheimer’s disease.” However, the clinical studies in the development program included a more specific patient population who had mild cognitive impairment (MCI) or mild Alzheimer’s disease. About a month after approval, the FDA revised the indication to specifically address the patient population studied, which included those with MCI or mild

- dementia. Patients in the clinical studies also had confirmation of elevated brain amyloid levels via positron emissions tomography (PET) scan.
- E. MCI is defined as the “symptomatic pre-dementia stage” on the continuum of cognitive decline and is characterized by objective impairment in cognition that is not severe enough to require help with usual activities of daily living. MCI is considered when there is concern regarding a change in cognition from the patient, caregiver, or clinician, objective evidence of impairment based on cognitive testing (e.g. memory, executive function, attention, language) and when there is preservation of independence in functional abilities and no evidence of significant impairment in social or occupational functioning.
 - F. Clinical characteristics suggestive that MCI is due to Alzheimer’s disease include the following:
 - a. Memory impairment is present
 - b. Progressive decline in cognition over months to years
 - c. Lack of Parkinsonism and visual hallucinations
 - d. Lack of vascular risk factors and extensive cerebrovascular disease on brain imaging
 - e. Lack of prominent behavioral or language disorders
 - G. Aducanumab (Aduhelm) was studied in two identically designed phase 3 trials (ENGAGE and EMERGE) which included a total of 3,285 patients with either MCI due to Alzheimer’s disease or mild Alzheimer’s disease dementia. An additional dose-ranging study, PRIME, was also used to support FDA-approval. All patients included in the ENGAGE and EMERGE clinical studies met the following baseline parameters for select cognitive function testing:
 - i. Clinical Dementia Rating (CDR) global score of 0.5; and
 - ii. Repeatable Battery for Assessment of Neuropsychological Status (RBANS) delayed memory index score ≤ 85 ; and
 - iii. Mini-Mental State Examination (MMSE) score of 24-30 were included in the study.
 - H. Further, all patients had objective evidence of cognitive impairment at screening. All patients also had amyloid pathology confirmed via PET scan. The age range of patients included in the clinical studies was 50-85 years. Further, patients were excluded from the trial if they had any medical or neurological condition (other than Alzheimer’s disease) that might be a contributing cause to the cognitive impairment, or brain hemorrhage, bleeding disorder, or cerebrovascular abnormalities.
 - I. Despite the identical trial design of ENGAGE and EMERGE, the results between the two studies were inconsistent. Both studies were terminated in March 2019 following a prespecified interim analysis that predicted that the trials would not meet their primary endpoints. Later, after reviewing the data further, it was announced that the prior analysis of EMERGE was incorrect and it had met its primary endpoint for a subset of patients, while ENGAGE did not. Results reported are analyzed based on the prespecified statistical analysis plan.
 - i. Primary Endpoint: The primary efficacy endpoint was the change from baseline on the CDR-Sum or Boxes (CDR-SB) following 78 weeks of treatment.
 - i. In the EMERGE study there was a statistically significant difference in change from baseline in CDR-SB in the high-dose treatment group compared to placebo (difference vs placebo -0.39 [95% CI -0.69 to -0.09]). Differences from placebo in the aducanumab (Aduhelm) low-dose group showed a numerical difference but were not statistically significant. The change in CDR-SB score in the high-dose group was less than the 1- to 2-point change that has been suggested as a minimal clinically important difference.
 - ii. In the ENGAGE study, no statistically significant difference was observed in the

- change from baseline in CDR-SB score following 78 weeks of treatment between the aducanumab (Aduhelm) and placebo groups.
- ii. Secondary Endpoint(s): Secondary efficacy endpoints included the change from baseline in MMSE score, change from baseline in the Alzheimer’s Disease Assessment Scale–Cognitive Subscale (13 items) (ADAS-Cog 13), and change from baseline in the Alzheimer’s disease Cooperative Study – Activities of Daily Living Inventory (Mild Cognitive Impairment version) (ADCS-ADL-MCI) score following 78 weeks of treatment.
 1. In the EMERGE study, statistically significant differences from placebo were observed in the high dose aducanumab (Aduhelm) group on all secondary endpoints evaluated.
 2. Secondary outcome results were not reported for the ENGAGE study.
- J. Multiple hypotheses have tried to explain the conflicting clinical trials results, but these remain exploratory at this time given that they were done post-hoc.
 - K. The safety of aducanumab (Aduhelm) was evaluated in 3,078 patients who received at least one dose of the medication. Pooled safety data show that 90.7% of patients receiving aducanumab (Aduhelm) vs 86.9% of placebo-treated patients experienced an adverse event (AE). The most common AEs included amyloid related imaging abnormalities (ARIA), headache, fall, and diarrhea. One patient in the aducanumab (Aduhelm) arm of an earlier phase trial died of an intracranial hemorrhage determined to be related to study treatment.
 - L. ARIAs are a common, dose-dependent effect of amyloid-targeting antibodies and can be divided into ARIA due to edema/effusion (ARIA-E) or bran microhemorrhage or localized superficial siderosis (ARIA-H). Given the mechanism of action, this was an AE of special interest. In the clinical trials titration over 24 weeks, baseline and follow-up MRIs, and dose suspensions were utilized to minimize the risk.
 - M. ARIA was common in the treatment groups, with over one-third of patients experiencing this adverse event. In the high-dose arm of ENGAGE and EMERGE, 41.3% of participants experienced ARIA compared to 10.3% in the placebo group.
 - N. Baseline MRI, followed by MRI prior to the 7th and 12th dose is recommended, since often times ARIA is asymptomatic.
 - O. Aducanumab (Aduhelm) should be discontinued when patients progress to moderate to severe Alzheimer’s disease since the medication has not been studied in more advanced settings. The following cognitive function scores (not all inclusive) represent moderate to severe impairment:
 - i. Clinical Dementia Rating (CDR) Global Score of 2 and above
 - ii. Mini Mental State Exam (MMSE) score of less than 19
 - iii. Montreal Cognitive Assessment (MoCA) score of 18 or less
 - iv. Quick Dementia Rating System (QDRS) score of 13 or less
 - P. Overall, the safety and efficacy of aducanumab (Aduhelm) remain highly uncertain based on conflicting phase 3 trial data and unknown relationship between clearance of amyloid plaques and clinical improvement in Alzheimer’s symptoms.
 - Q. Since there are no proven disease modifying or curative therapies for Alzheimer’s disease to date, major advocacy and government bodies, such as the National Institutes of Health, U.S. Department of Health and Human Services, and the respective federal government portal of resources on Alzheimer’s and related dementias at Alzheimers.gov, direct to clinical trial participation. Patients participating in clinical trials receive regular care, often at leading health care facilities with experts in the field while participating in important medical research and further advancements in treatment with close safety monitoring and follow-

up. Participation in a clinical trial remains the most favorable treatment option for patients with Alzheimer’s disease when available. At this time, the most likely place someone with Alzheimer’s will be cured, is within the setting of a clinical trial.

- R. The following resources provide extensive information on available clinical trials for those with Alzheimer’s disease:
 - i. <http://www.nia.nih.gov/alzheimers/clinical-trials>
 - ii. https://www.alz.org/alzheimers-dementia/research_progress/clinical-trials
 - iii. <https://clinicaltrials.gov>

VI. Dosage/Administration

Indication	Dose	
Alzheimer’s disease	Initial titration schedule:	
	IV Infusion (every 4 weeks)	Dosage (administered over approx. one hour)
	Infusion 1 and 2	1 mg/kg
	Infusion 3 and 4	3 mg/kg
	Infusion 5 and 6	6 mg/kg
	Infusion 7 and beyond	10 mg/kg
After initial titration, the recommended dosage is 10 mg/kg every four weeks and at least 21 days apart.		

VII. Billing Code/Availability Information

Jcode:

- J3590 – Unclassified drugs
- C9399 – Unclassified drugs or biologics (hospital outpatient use)

NDC:

- 170 mg/1.7 mL (100 mg/mL) single-dose vial – NDC 64406-101-01
- 300 mg/3 mL (100 mg/mL) single-dose vial – NDC 64406-102-02

VIII. References

1. Aduhelm [package insert]. Cambridge, MA; Biogen Inc; July 2021.
2. Product Dossier. “Unapproved Product Formulary Submission Dossier: Aducanumab in Mild Cognitive Impairment due to Alzheimer’s Disease and Alzheimer’s Disease Dementia. Biogen Inc. September 5, 2020.
3. McKhann M.G. et al. The diagnosis of dementia due to Alzheimer’s disease: Recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. *Alzheimers Dement.* 2011 May; 7(3): 263-269.
4. Lin GA, Whittington MD, Synnott PG, McKenna A, Campbell J, Pearson SD, Rind DM. Aducanumab for Alzheimer’s Disease: Effectiveness and Value; Draft Evidence Report. Institute

for Clinical and Economic Review, May 5, 2021. <https://icer.org/assessment/alzheimers-disease-202>

5. Langa, LM, Levine DA. The Diagnosis and Management of Mild Cognitive Impairment: A clinical Review
6. Alzheimer's Home Page: National Institute on Aging. Alzheimers.gov. <https://www.alzheimers.gov/>. Accessed on July 16, 2021.
7. Participating in Alzheimer's disease Research. National Institute on Aging. <https://www.nia.nih.gov/health/participating-alzheimers-disease-research>. Accessed on July 16, 2021.