

## Aduhelm™ (aducanumab-avwa)

Date of Origin: 06/23/2021

Last Review Date: 06/23/2021

Effective Date: 06/23/2021

Dates Reviewed: 06/23/2021

Developed By: Medical Criteria Committee

### I. Length of Authorization

N/A

### II. Dosing Limits

N/A

### III. Initial Approval Criteria

Aducanumab (Aduhelm) is considered **Experimental or Investigational** for the treatment of Alzheimer's disease as defined by a treatment for which scientific or medical assessment has not been completed, or the effectiveness of the treatment has not been generally established. For more information, please reference the member handbook.

### IV. Renewal Criteria

N/A

### V. Supporting Evidence

- I. Aducanumab (Aduhelm) is indicated for the treatment of Alzheimer's 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.
- II. 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.
- III. 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.

- IV. Although the FDA broadly approved the use of aducanumab (Aduhelm) for “the treatment of Alzheimer’s disease,” the clinical studies in the development program included a more specific patient population who had mild cognitive impairment (MCI) or mild Alzheimer’s disease. Patients in the clinical studies also had confirmation of elevated brain amyloid levels via positron emissions tomography (PET) scan.
- V. Mild cognitive impairment (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.
- VI. 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
- VII. 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. In the ENGAGE and EMERGE trials, patients with a Clinical Dementia Rating (CDR) global score of 0.5, a Repeatable Battery for Assessment of Neuropsychological Status (RBANS) delayed memory index score  $\leq$  85, and a Mini-Mental State Examination (MMSE) score of 24-30 were included in the study. 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.
- VIII. 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 more closely, 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.
  - a. Primary Endpoint: The primary efficacy endpoint was the change from baseline on the CDR-Sum of 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.
- b. 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.
  - i. In the EMERGE study, statistically significant differences from placebo were observed in the high dose aducanumab (Aduhelm) group on all secondary endpoints evaluated.
  - ii. Secondary outcome results were not reported for the ENGAGE study.
- IX. 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.
- X. 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.
- XI. 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.
- XII. 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.
- XIII. Baseline MRI, followed by MRI prior to the 7<sup>th</sup> and 12<sup>th</sup> dose is recommended, since often times ARIA is asymptomatic.
- XIV. Overall, the safety and efficacy of aducanumab (Aduhelm) remain highly uncertain based on conflicting phase 3 trail data and unknown relationship between clearance of amyloid plaques and clinical improvement in Alzheimer's symptoms.

## 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:

- J3490 – 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; June 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