PRIOR AUTHORIZATION POLICY

POLICY: Neurology – Aduhelm Prior Authorization Policy
- Aduhelm™ (aducanumab-avwa intravenous infusion – Biogen/Eisai)

REVIEW DATE: 06/16/2021

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 6.2 million Americans ≥ 65 years of age are living with Alzheimer's dementia in 2021, with 72% of these people ≥ 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 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. 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 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] 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 to 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.[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.

Dosing Information

Aduhelm is titrated up to the recommended dose of 10 mg/kg over 6 months.[1] Aduhelm is administered every 4 weeks as an intravenous infusion given over 1 hour. Dosing of Aduhelm is initiated at 1 mg/kg for infusions one and two, increased to 3 mg/kg for infusions three and four, increased to 6 mg/kg for infusions five and six, and increased to 10 mg/kg for infusion seven and beyond. Aduhelm has not demonstrated efficacy when titrated to a maximum dose of 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 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).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Aduhelm. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Aduhelm as well as the monitoring required for adverse events and long-term efficacy, approval requires Aduhelm to be prescribed by a neurologist.

Documentation: Documentation is required for use of Aduhelm as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Aduhelm is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Alzheimer's Disease.** Approve for the duration noted if the patient meets ONE of the following criteria (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets EACH of the following (i through x):
     - **i.** Patient is ≥ 50 years of age and < 85 years of age; AND
     - **ii.** Patient has a Clinical Dementia Rating-Global Score of 0.5 (very mild dementia) or 1 (mild dementia) **[documentation required]**; AND

iii. Patient has a Mini-Mental State Examination (MMSE) score between ≥ 24 and ≤ 30 **[documentation required]**; AND

iv. Patient meets BOTH of the following criteria (a and b):

a) Patient has had magnetic resonance imaging (MRI) of the brain within the past 1 year **[documentation required]**; AND

b) The MRI showed BOTH of the following (1 and 2):

(1) No pre-treatment localized superficial siderosis, fewer than ten brain microhemorrhages, and if present, brain hemorrhage < 1 cm **[documentation required]**; AND

(2) Medical or neurological conditions, other than Alzheimer's disease, that may be contributing to the patient's cognitive impairment were ruled out **[documentation required]**; AND

v. Patient has had a positive test for amyloid beta based on a Positron Emission Tomography (PET) scan **[documentation required]**; AND

vi. If the patient is concomitantly taking medications to treat Alzheimer's disease, the dose(s) must be stable for at least 8 weeks prior to initiating Aduhelm **[documentation required]**; AND

vii. Patient does NOT have a clinically significant unstable psychiatric illness; AND

viii. Patient does NOT have a history of brain hemorrhage, bleeding disorder, or cerebrovascular abnormalities; AND

ix. Patient is NOT taking anticoagulant or antiplatelet agents (except aspirin for prevention of cardiovascular or thromboembolic events); AND

Note: Anticoagulant or antiplatelet agents include Pradaxa (dabigatran capsules), Savaysa (edoxaban tablets), Eliquis (apixaban tablets), Xarelto (rivaroxaban tablets), warfarin, low-molecular-weight heparins (enoxaparin sodium injection, Fragmin® [dalteparin sodium injection]), fondaparinux sodium injection, prasugrel hydrochloride tablets, clopidogrel tablets, or Brilinta (ticagrelor tablet).

x. The medication is prescribed by a neurologist.

B) Patient is Currently Receiving Aduhelm. Approve for 6 months if the patient meets EACH of the following (i through vi):

i. Patient is ≥ 50 years of age; AND

ii. Patient has not progressed beyond a Clinical Dementia Rating-Global Score of 1 **[documentation required]**; AND

iii. Patient is able to tolerate a Aduhelm maintenance dose of 10 mg/kg every 4 weeks; AND

iv. Patient meets the following (a and b):

a) If the patient has received six infusions of Aduhelm, the patient has had an MRI of the brain prior to the 7th infusion (first dose of 10 mg/kg) of Aduhelm to determine if the patient has developed amyloid related imaging abnormalities (ARIA) **[documentation required]**; AND

b) If the patient has received eleven infusions of Aduhelm, the patient has had an MRI of the brain prior to the 12th infusion (sixth dose of 10 mg/kg) of Aduhelm to determine if the patient has developed ARIA **[documentation required]**; AND

v. If an MRI confirms ARIA, the patient meets ONE of the following (a or b):

a) Patient meets BOTH of the following (i and ii):

i. Patient has fewer than ten new incident microhemorrhages **[documentation required]**; AND

ii. Patient has two or fewer focal areas of superficial siderosis (radiographic severe ARIA-H) **[documentation required]**; OR

b) Patient has had a clinical evaluation and a follow-up MRI demonstrating radiographic stabilization (i.e., no increase in size or number of amyloid related imaging abnormalities-

hemosiderin deposition [ARIA-H]) prior to continuing treatment **[documentation required]**; AND

vi. The medication is prescribed by a neurologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Aduhelm is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Aduhelm™ intravenous infusion [prescribing information]. Cambridge, MA: Biogen; June 2021.
2. Alzheimer's Association. Alzheimer's disease facts and figures-2021. Available at: https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf. Accessed on June 7, 2021.
3. Data on file. Unapproved Product Formulary Submission Dossier: Aducanumab in Mild Cognitive Impairment due to Alzheimer's Disease and Alzheimer's Disease Dementia. Biogen. Received April 2021.
4. Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee Meeting. Combined FDA and Applicant PCNS Drugs Advisory Committee Briefing Document. November 6, 2020.
5. Alexander GC, Emerson S, Kesselheim AS. Evaluation of aducanumab for Alzheimer Disease scientific evidence and regulatory review involving efficacy, safety, and futility. *JAMA*. Published online March 30, 2021.