DR.011.A	Aduhelm™ (aducanumab-avwa)	Health Partners Plans

Title: Aduhelm™ (aducanumab-avwa)	**Original Implementation Date:** 11/1/2021
Policy #: DR.011.A	**Version Date [A]:** 11/1/2021
Type: Medical	**Last reviewed date:** 9/15/2021
Sub-Type: Drug (DR)	**30 day notification:** 10/1/2021

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PRODUCT VARIATIONS

This policy only applies to ALL Health Partners Plans (HPP) product lines unless listed below.

FDA APPROVED INDICATIONS

Aduhelm™ is an amyloid beta-directed antibody indicated for the treatment of:

- Alzheimer's disease
  - This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with ADUHELM. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

OFF-LABELED USE

Authorization for off-labeled use of medication will be evaluated on an individual basis. Review of an off-labeled request by the Medical Staff will be predicated on the appropriateness of treatment and full consideration of medical necessity. For off-label use Medical Directors will review scientific literature and local practice patterns.

PRIOR AUTHORIZATION CRITERIA

Initial Criteria

1) Is the patient 50 years old or older? *If YES, go to 3. If NO, go to 2.*

2) Does the patient have documentation of a genetic mutation and/or documentation of Alzheimer's disease? *(Documentation must be attached) If YES, go to 3. If NO, refer to Medical Director.*

3) Does the patient have documentation of a diagnosis of Alzheimer's disease of mild severity (a MMSE score between 24 and 20 or a CDR-SB score of 0.5 to 1) *(Documentation must be attached) If YES, go to 4. If NO, refer to Medical Director.*

4) Does the patient have any contraindications to the requested drug or it's components (history of hypersensitivity to ADUHELM ™)? *If NO, go to 5. If YES, refer to Medical Director.*

5) Does the patient have any medical or neurological condition that may be contributing to cognitive impairment? *If NO, go to 6. If YES, refer to Medical Director.*

6) Has the patient had a stroke, TIA, or unexplained loss of consciousness in the past year? *If NO, go to 7. If YES, refer to Medical Director.*

7) Does the patient have a history of unstable angina, MI, advanced chronic HF, or clinically significant conduction abnormalities for $\geq$ 1 year? *If NO, go to 8. If YES, refer to Medical Director.*

8) Does the patient have brain hemorrhage, bleeding disorder, cerebrovascular abnormalities or on blood thinners other than prophylactic dose aspirin? *If NO, go to 9. If YES, refer to Medical Director.*

9) Does the patient have a recent (within the last year) PET scan showing presence of beta-amyloid plaque and/or CSF testing, showing presence of tau protein? (Attach results) *If YES, go to 10. If NO, refer to Medical Director.*

10) Is the medication prescribed by or in consultation with a physician who is a psychiatrist, neurologist, or neuropsychiatrist? *If YES, go to 11. If NO, refer to Medical Director.*

11) Have all other causes of dementia been ruled out? (vascular dementia, Lewy body dementia (DLB), Frontotemporal dementia (FTD), Parkinson's disease dementia)? *If YES, go to 12. If NO, refer to Medical Director.*

12) Will the patient be dosed using the following dosing schedule? *If YES, go to 13. If NO, refer to Medical Director.*

IV Infusion (every 4 weeks)	**ADUHELM Dosage (administered over approximately 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

13) Does the patient have a recent MRI scan (within one year)? (Attach results) *If YES, approve for 6 months. If NO, refer to Medical Director.*

RENEWAL CRITERIA

1) Does the patient continue to meet the diagnostic criteria after initial treatment of ADUHELM™ for Alzheimer's? *If YES, go to 2. If NO, refer to Medical Director.*

2) Does the patient have the absences of unacceptable toxicity which precludes safe administration of the drug? (Examples of unacceptable toxicity include the following: ARIA-E (cerebral edema), ARIA-H microhemorrhage (small heamorrhages in the brain) and/or superficial siderosis (deposition of excess iron), fall, etc.) *If YES, go to 3. If NO, refer to Medical Director.*

3) Does the patient have an MRI after the 6th dose showing 10 or more new incident microhemorrhages or > 2 focal areas of superficial siderosis (radiographic severe ARIA-H) and is showing radiographic stabilization (i.e., no increase in size or number of ARIA-H)? (attach results) *If YES and patient has been on treatment for less than 12 months, approve for 6 months. If YES and patient has been on treatment for longer than 12 months, go to question 4. If NO, refer to Medical Director.*

4) If the patient has been on the treatment for greater than 12 months has the patient shown clinical benefit (stabilization)? (Attach notes) *If YES, approve for 6 months. If NO, refer to Medical Director.*

BACKGROUND

Alzheimer's disease

Alzheimer's disease is a neurodegenerative disorder resulting in progressive cognitive and behavioral decline. Alzheimer's disease is the leading cause of dementia, a general term for memory loss and cognitive decline, accounting for 60% to 80% of cases. Estimating to affect 5.8 million Americans, or 10% if people 65 years old or older, with 80% being older than 75 years old. Additionally, 200,000 Americans have early-onset Alzheimer's disease, defined as Alzheimer's disease affecting those younger than 65 years old. Due to the aging population, the estimated number of people age 65 years and older with Alzheimer's disease is estimated to be 13.8 million in the United States in 2050, barring any developments in therapies. Alzheimer's disease is the sixth leading cause of death in the United States and the fifth leasing cause of death among those age 65 years and older. Almost two-thirds of Americans with Alzheimer's disease are women. African Americans and Latino Americans are twice as likely and one and half times as likely, respectively to have Alzheimer's disease as older White Americans. On average, patients survive approximately 4 to 8 years after diagnosis, with survival time affected by age at diagnosis and severity of other medical conditions.

The pathogenesis of Alzheimer's disease has been attributed to extracellular aggregates of beta-amyloid plaques and intracellular neurofibrillary tangles in the cortical and limbic areas of the human brain. Beta-amyloid peptides are created through the proteolytic cleavage of the amyloid precursor protein; this process likely instigates the intraneuronal accumulation of phosphorylated tau, which is the primary component of the neurofibrillary tangles. It is estimated that beta-amyloid plaques begin to develop 10 years to 30 years before Alzheimer's disease onset, while neuronal degeneration, such as the presence of tau in the cerebrospinal fluid, may develop shortly before clinical symptoms first appear. Both biomarkers of Alzheimer's disease can be detected in the CSF and by positron emission computed tomography (PET).

Aside from increasing age, which is the greatest risk factor for Alzheimer's disease, the two other major risk factors are family history and genetics (risk genes and deterministic genes, the latter being genes that cause the disease rather than genes that increase the risk for disease development). Familial Alzheimer's disease has mainly been associated with mutation in APP and presenilin genes PSEN1 and PSEN2/ Comparatively, non-familial or sporadic-onset Alzheimer's disease has a complex etiology, involving genetic, environmental, metabolic, viral, and other factors. The E4 variant of apolipoprotein E is the main susceptibility gene for Alzheimer's disease, while the E2 variant of APOE is considered a protective factor that reduces the incidence of Alzheimer's disease and beta-amyloid accumulation and delays the age of Alzheimer's disease onset. Acquired risk factors include but are not limited to head trauma, hypertension, cerebrovascular disease, hypercholesteremia, and environment risk factors (lead, pesticides). Conversely, higher education and socioeconomic status have been associated with lower age-adjusted incidence of Alzheimer's disease diagnosis.

Alzheimer's disease is characterized by memory loss and progressive neurocognitive dysfunction. Signs and symptoms include memory loss that disrupts daily life; challenges in planning or problem-solving; difficulty completing familiar tasks at home, work, or at leisure; confusion with orientation to time or place; difficulty with visual images and spatial relationships; difficulties with speaking or writing; decreased or poor judgment; withdrawal from work or social activities; and changes in mood and personality/ Individuals may present with one or more of these symptoms and in varying degree of severity, as listed below.

1. Clinical Dementia Rating (CDR)-Global Score
    a. 0 = Normal
    b. 0.5 = Very Mild Dementia
    c. 1 = Mild Dementia
    d. 2 = Moderate Dementia
    e. 3 = Severe Dementia
2. Mini-Mental Examination Status (MMSE)
    a. 25 - 30 suggest normal cognition
    b. 20 – 24 suggests mild dementia
    c. 13 – 20 suggests moderate dementia
    d. Less than 12 suggests severe dementia
3. Montreal Cognitive Assessment (MoCA)
    a. Mild Cognitive Impairment: 19 – 25
    b. Mild Alzheimer's Disease: 11 – 21
    c. Normal: 26 and above

DOSAGE AND ADMINISTRATION

Single-use dose vial containing 170mg/1.7mL or 300mg/3mL of aducanumab-avwa as a solution. Dilution in 100mL of 0.9% Sodium Chloride Infused through an IV line containing a sterile, low-protein binding, 0.2 or 0.22 micron in-line filter, is required.

Dosing recommendations for Alzheimer's disease:

- After an initial titration, the recommended dosage of ADUHELM is 10 mg/kg (see Table 1). ADUHELM is administered as an intravenous (IV) infusion over approximately one hour every four weeks and at least 21 days apart.

IV Infusion (every 4 weeks)	**ADUHELM Dosage (administered over approximately 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

RISK FACTORS/SIDE EFFECTS

- **Amyloid Related Imaging Abnormalities (ARIA)** Enhanced clinical vigilance for ARIA is recommended during the first 8 doses of treatment with ADUHELM™, particularly during titration. If a patient experiences symptoms which could be suggestive of ARIA (eg, headache, altered mental status, dizziness, visual disturbance, nausea), clinical evaluation should be performed, including MRI testing if indicated.
- **Hypersensitivity Reactions**: Angioedema and urticaria have occurred. If a hypersensitivity reaction occurs, promptly discontinue the infusion of ADUHELM and initiate appropriate therapy.

BLACK BOX WARNING

N/A

MONITORING

Efficacy

- Physical Findings
  - MMSE score (Mini0Mental State Examination)
  - CDS-SB (Clinical Dementia Rating-Sum of Boxes)
  - ADAS-Cog 13 (Alzheimer's disease Assessment Scale-Cognitive Subscale 13)
  - Aβ PET composite SUVR (Beta-amyloid positron emission tomography standardized uptake value ratio)

Safety

- Look for sign and symptoms stated above in Risk Factors/Side Effects section to ensure safety.

CODING

Note: The Current Procedural Terminology (CPT®), Healthcare Common Procedure Coding System (HCPCS), and the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes that may be listed in this policy are for reference purposes only. Listing of a code in this policy does not imply that the service is covered and is not a guarantee of payment. Other policies and coverage guidelines may apply. When reporting services, providers/facilities should code to the highest level of specificity using the code that was in effect on the date the service was rendered. This list may not be all inclusive.

CPT Code	Description
99483	Cognition-focused evaluation including a pertinent history and examination

HCPCS Code	Description
J3590	Aduhelm (aducanumab-avwa)
G0336	PET imaging brain Alzheimer's

ICD 10 Code	Description
G30	Alzheimer's disease
G30.0	Alzheimer's disease with early onset
G30.1	Alzheimer's disease with late onset

POLICY HISTORY

Summary	Version	Version Date
This is a new drug policy.	A	11/1/2021

REFERENCES

1. Aduhelm. Prescribing information. Biogen; June 2021. Accessed July 9, 2021.
2. Albert M, DeKosky S, Dickson D, et al. The diagnosis of mild cofnitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging- Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Azlheimers Dement. 2011; 7(3): 270-279. Doi:10.1016/j.jalz.2011.03.008.
3. Alzheimer's Association (AA). Causes and risk factors for Alzheimer's disease. Accessed July 8, 2021c. https://www/alz.org/alzheimers-dementia/what-is-alzheimers/causes-and-risk-factors.
4. Clinicaltrials.gov. 221AD301 Phase 3 Stude of Aducanumab (BIIB037) in Early Alzheimer's Disease (ENGAGE). Updated August 14,2020 Accessed July 8, 2021. https://clinicaltrials.gov/ct2/show/NCT02477800.
5. Clinicaltrials.gov. 221AD302 Phase 3 Stude of Aducanumab (BIIB037) in Early Alzheimer's Disease (EMERGE). Updated may 6, 2021 Accessed July 8, 2021. https://clinicaltrial.gov/ct2/show/NCT02484547.