PART B DRUG MEDICAL/PHARMACY	ASPIRE HEALTH	**Effective Date** January 1, 2024	
	ADUHELM (ADUCANUMAB)	**Policy #** Aduhelm (aducanumab)	
		Review Date 11/29/2023	**Applicable to:** ☑ Medicare Advantage ☐ Commercial ☐ Elevance Health HMO ☐ Blue Shield Trio
	Approver's Name & Title QI & UM Drug Subcommittee		

Aspire Health Plan (AHP) applies medical drug clinical criteria as a reference for medical policy information only. Federal and state laws or requirements, contract language, and Plan benefit may take precedence over the application of these clinical criteria. Please consult the applicable certificate or contract for benefit details. This policy is subject to revision at the discretion of the Plan and is therefore subject to change. Refer to the disclaimer section below for more information.

POLICY

This policy addresses the coverage of Aduhelm (aducanumab) in the treatment of treatment of Alzheimer's disease (AD), specifically, according to the labeled indication, in "patients with mild cognitive impairment or mild dementia stage of disease, with confirmed presence of amyloid beta pathology prior to treatment initiation."

Aspire Health Plan (AHP) adheres to Medicare guidelines and coverage determinations will be in compliance with the National Coverage Determination (NCD) issued by CMS effective 12/12/2022 and located on the CMS website at: Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (AD)

APPLICABLE HCPCS

J0172 (Injection, aducanumab-avwa, 2 mg) (Effective 1/1/2022)

Available Dosage Form: injection as 170 mg/1.7 mL (100 mg/mL) and 300 mg/3 mL (100 mg/mL) solution in single-dose vials for intravenous use only.

CLINICAL CRITERIA

A. INITIAL CRITERIA

Aduhelm (aducanumab) may be authorized when **ALL** of the following criteria outlined in CMS National Coverage Determination 200.3 'Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (AD)' (Published April 7, 2022), including:

1. Enrollment in an FDA-approved randomized controlled trial or a clinical trial supported by the NIH (National Institutes of Health)

B. REAUTHORIZATION / CONTINUATION OF THERAPY CRITERIA

Aduhelm (aducanumab) may be authorized when **ALL** of the following criteria have been met with documentation as outlined in CMS National Coverage Determination 200.3 Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (AD) (Published April 7, 2022), including:

1. Enrollment in an FDA-approved randomized controlled trial or a clinical trial supported by the NIH (National Institutes of Health)

C. EXCLUSIONS

Aduhelm (aducanumab) will not be authorized in ANY of the following cases:

1. Member does not meet ALL criteria as as outlined in CMS National Coverage Determination 200.3 Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (AD) (Published April 7, 2022).

2. Experimental/Investigational Use: *Medically accepted indications not supported by CMS recognized compendia or acceptable peer-reviewed literature.

   *Medically accepted indications are defined by CMS as those uses of a covered drug that are approved under the federal Food, Drug and Cosmetic Act, or the use of which is supported by one or more citations included or approved for inclusion in any of the compendia described in section 1927(g)(1)(B)(i) of the Act. These compendia guide review of off-label and off-evidence prescribing and are subject to minimum evidence standards for each compendium. Currently, this review includes the following references when applicable and may be subject to change per CMS:
   - American Hospital Formulary Service-Drug Information (AHFS-DI)
   - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
   - Truven Health Analytics Micromedex DrugDEX
   - Elsevier/Gold Standard Clinical Pharmacology
   - Wolters Kluwer Lexi-Drugs

STEP THERAPY

Step Therapy: NOT APPLICABLE

DOSAGE AND AUTHORIZATION TIMEFRAMES

1. Recommended Dose (maintenance dosage): 10 mg/kg administered as an intravenous (IV) infusion over approximately one hour every four weeks
   - Aduhelm is titrated up to the recommended dose of 10 mg/kg over 6 months. Aduhelm is given every 4 weeks as an IV infusion given over 1 hour.
   - Dosing of Aduhelm is initiated at 1 mg/kg for infusions one and two, then 3 mg/kg for infusions three and four, then 6 mg/kg for infusions five and six, and 10 mg/kg for infusion seven and beyond.
   - Aduhelm has not demonstrated efficacy when titrated to a maximum dose 3 or 6 mg/kg. Doses of 10 mg/kg were required in order to show effectiveness.

2. Quantity: N/A

3. Authorization Period: N/A

DRUG INFORMATION

PHARMACOLOGIC CATEGORY: Anti-Amyloid Monoclonal Antibody; Immune Globulin; Monoclonal Antibody

ROUTE OF ADMINISTRATION: Intravenous Infusion

FDA-APPROVED INDICATIONS: Alzheimer disease

Treatment of Alzheimer disease in patients with mild cognitive impairment or mild dementia stage of disease, with confirmed presence of amyloid beta pathology prior to treatment initiation.

COMPENDIAL APPROVED OFF-LABELED USES: None
Off-Label / Investigational Uses: Requests for off-label uses with a paucity of clinical evidence, or uses that are not generally accepted by the medical community (such as professional guidelines or consensus), CMS-recognized compendia, or peer-reviewed literature is considered investigational and will not be authorized due to insufficient evidence of overall therapeutic value of safety and efficacy.

BOXED WARNING

Amyloid-Related Imaging Abnormalities (ARIA)
Monoclonal antibodies directed against aggregated forms of beta amyloid, including aducanumab, can cause amyloid related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E) and ARIA with hemosiderin deposition (ARIA-H). Incidence and timing of ARIA vary among treatments. ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events rarely can occur. Serious intracerebral hemorrhages, some of which have been fatal, have been observed in patients treated with this class of medications.

ApoE ε4 homozygotes
Patients who are apolipoprotein E ε4 (ApoE ε4) homozygotes (~15% of AD patients) treated with this class of medications, including aducanumab, have a higher incidence of ARIA, including symptomatic, serious, and severe radiographic ARIA, compared to heterozygotes and noncarriers. Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. Prior to testing, prescribers should discuss with patients the risk of ARIA across genotypes and the implications of genetic testing results. Prescribers should inform patients that if genotype testing is not performed they can still be treated with aducanumab; however, it cannot be determined if they are ApoE ε4 homozygotes and at higher risk for ARIA.

Consider the benefit of aducanumab for the treatment of AD and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment with aducanumab.

CONTRAINDICATIONS
There are no contraindications listed in the manufacturer's labeling.

OTHER CONSIDERATIONS
Dosage and administration instructions outlined in the label include the following:

- Confirm the presence of amyloid beta pathology using PET or lumbar puncture prior to initiating treatment;
- Titration is required for treatment initiation;
- Prior to initiation: Confirm the presence of amyloid beta pathology.
- Monitor closely for clinical and MRI changes
- Monitor for ARIA-E and ARIA-H: Obtain brain MRI ***prior (recent) to*** initiating treatment, ***prior to*** the 5th infusion (first dose of 6 mg/kg), 7th infusion (first dose of 10 mg/kg), 9th infusion (third dose of 10 mg/kg), and 12th infusion (6th dose of 10 mg/kg).
- If radiographically observed ARIA occurs, treatment recommendations are based on type, severity,

and presence of symptoms (e.g., headache, altered mental status, dizziness, visual disturbance, seizure, nausea);
- MRI as indicated if ARIA symptoms present or asymptomatic ARIA observed (manufacturer's labeling).

CLINICAL SUMMARY / APPENDIX

Alzheimer dementia (AD) is a gradual progressive impairment in cognition and memory, that typically affects adults aged ≥ 65 years and interferes with function and daily activities. AD progresses on a continuum categorized by three phases: (1) preclinical AD (2) mild cognitive impairment (MCI) due to AD and (3) Alzheimer's dementia, which is further, classified into mild, moderate, and severe. As the disease progresses, noticeable symptom changes occur in memory, thinking, and behavioral, impacting the patient's ability to perform activities of daily living. Risk factors for late-onset AD include older age, mutations in the apolipoprotein e4 gene (APOE-e4), and family history of AD. Early-onset AD has been linked to several less common genetic mutations. No single test is used to diagnose Alzheimer's dementia but rather a variety of assessments, cognitive tests, and biomarkers collectively assist in making the diagnosis. Current treatment options for AD focus on supportive management and includes the treatment of dementia with medications that are not disease-modifying (e.g., donepezil, rivastigmine, galantamine, memantine, etc.). Aducanumab promotes the clearance of beta-amyloid plaques from the brain; however, the role of beta-amyloid protein in disease is not well understood.

Aduhelm (aducanumab-avwa) is a recombinant human immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta, which is potentially a disease-modifying treatment. The accumulation of amyloid beta plaques in the brain is a defining pathophysiological feature of Alzheimer's disease. Aduhelm reduces amyloid beta plaques in the brain, which is theorized to slow disease progression.

Aduhelm (aducanumab) is indicated for the treatment of Alzheimer's disease. Treatment with Aduhelm should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. **There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied.**

Approval for this indication was granted under the FDA accelerated approval process based on reduction in amyloid beta plaques (a surrogate end point) in patients treated with aducanumab-avwa in clinical trials; continued approval may be contingent upon verification of clinical benefit in confirmatory trials, which are not anticipated to be completed until 2029. Long-term clinical efficacy has not been demonstrated. Conflicting evidence is available from two randomized controlled trials that were terminated for futility and included significant protocol amendments and a controversial statistical analysis.

The efficacy of aducanumab, supporting its FDA approval, was evaluated in two identical, Phase 3 randomized clinical trials, ENGAGE (Study 301, Study 2, NCT02477800) and EMERGE (Study 302, Study 1, NCT02484547).

- ENGAGE and EMERGE randomized patients (who had a positive amyloid PET scan) with mild cognitive impairment (MCI) or mild dementia due to AD to low or high dose aducanumab, or placebo.
  - *MCI is associated with minor changes in cognition and short-term memory loss, mild but detectable functional impairment and no significant impairment in social or occupational functioning. Mild AD is associated with noticeable lapses in memory and possible difficulty with activities of daily living (ADL) but with preserved ability to function independently*
- Approximately halfway through the two Phase 3 studies, a planned interim analysis met pre-specified 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).
  - *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.

- Efficacy was not demonstrated in the low-dose arm of EMERGE or in either treatment arm of ENGAGE.

ARIA, the most common adverse event, requires MRI monitoring before and during therapy, as well as close clinical monitoring.

Professional Society Guidelines

Aduhelm is has been not addressed in guidelines or consensus. The current American Academy of Neurology (AAN) guideline on mild cognitive impairment was published in 2018 (reaffirmed January 2021), prior to the approval of Aduhelm.

REFERENCES

Government Agency

1. Centers for Medicare and Medicaid Services (CMS). Medicare coverage database: National coverage determination (NCD) (search: Aduhelm, aducanumab). Available from CMS: Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (AD)**.**
2. Centers for Medicare & Medicaid Services (CMS). Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (CAG-00460N). Decision Memorandum. Baltimore, MD: CMS; April 7, 2022.
3. Food and Drug Administration. Buracchio TJ, Yasuda SJ, Bastings E, Dunn B. Aducanumab: Summary memorandum. Published June 7, 2021. Accessed at: FDA
4. Food and Drug Administration. Dunn B. BLA approval letter: Aduhelm (aducanumab-avwa) (BLA 761178). Published June 7, 2021. Accessed at: FDA
5. ClinicalTrials.gov identifier: NCT02484547. Biogen. 221AD302 phase 3 study of aducanumab (BIIB037) in early Alzheimer's disease (EMERGE). Updated May 6, 2021. Accessed at: https://clinicaltrials.gov/ct2/show/NCT02484547
6. ClinicalTrials.gov identifier: NCT02477800. Biogen. 221AD301 phase 3 study of aducanumab (BIIB037) in early Alzheimer's disease (ENGAGE). Updated August 14, 2020. Accessed at: https://clinicaltrials.gov/ct2/show/study/NCT02477800

Prescribing Information

1. Aduhelm (aducanumab) [prescribing information]. Cambridge, MA: Biogen Inc; August 2023.
2. U.S. Food and Drug Administration (FDA). FDA grants accelerated approval for Alzheimer's drug. Press Release. Silver Spring, MD: FDA; June 7, 2021.

Peer Reviewed Literature, Guidelines

1. Alexander GC, Emerson S, Kesselheim AS. Evaluation of aducanumab for Alzheimer Disease scientific evidence and regulatory review involving efficacy, safety, and futility. JAMA. 2021;325(17):1717-1718.
2. 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.
3. Petersen RC, Lopez O, Armstrong MJ, et al. Practice guideline update summary: mild cognitive impairment: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2018;90:126-35

IMPORTANT REMINDER

This Medicare Part B Step Therapy Medical Necessity Guideline is provided for informational purposes only and neither constitutes nor replaces professional medical advice. Physicians, hospitals, and other providers are expected to administer or use drugs/biologicals in the most effective and clinically appropriate manner. Treating physicians and other health care providers are solely responsible for all medical care decisions. In accordance with the member's Evidence of Coverage (EOC), every benefit plan has its own coverage provisions, limitations, and exclusions. In the event of a conflict between this policy and the member's EOC, the member's EOC provisions will take precedence.

Aspire Health Plan (AHP) adheres to Medicare guidelines, including National Coverage Determination (NCD), Local Coverage Determinations (LCDs), Local Coverage Articles (LCAs), and other relevant Medicare manuals established by CMS. Compliance with these guidelines is required when applicable. Refer to the CMS website at http://www.cms.hhs.gov. For the most up-to-date Medicare policies and coverage, please search the Medicare Coverage Database. All LCDS are the same for each state within a Jurisdiction. Medicare Part B Administrative Contractor (MAC) for CA [Jurisdiction E (1)]: Active LCDs - JE Part B – Noridian (noridianmedicare.com). In the event of a discrepancy between this policy and the Medicare NCD or LCD, the Medicare NCD/LCD will govern.

This policy is utilized by AHP to determine coverage in the absence of applicable CMS Medicare guidelines. Please refer to the links provided in the References section below to access the Medicare source materials that were used for developing this resource document. This document does not serve as a substitute for the official Medicare source materials that provide detailed information on Medicare coverage requirements. In the event of a conflict between this document and Medicare source materials, the Medicare source materials will take precedence.

The inclusion of a code in this policy does not imply that the health service it describes is covered or not covered. Benefit coverage for health services is determined by the member-specific plan document and applicable laws that may mandate coverage for a particular service. Inclusion of a code does not imply or guarantee reimbursement or payment of a claim. Other Policies and Standards may also apply. Providers are expected to retain or have access to the necessary documentation when requested in order to support coverage.

POLICY HISTORY

Version	Date	Revision Author/Title	Summary of Changes
1	11/29/2023		New Policy