

Aduhelm (aducanumab-avwa)
PAM-042

Iowa Medicaid Program:	Prior Authorization	Effective Date:	01/01/2022
Revision Number:	2	Last Rev Date:	10/20/2023
Reviewed By:	Medicaid Medical Director	Next Rev Date:	10/18/2024
Approved By:	Medicaid Clinical Advisory Committee	Approved Date:	10/21/2022

Overview

Medication: ¹	aducanumab-avwa
Brand Name:	Aduhelm [®]
Pharmacologic Category:	Anti-amyloid monoclonal antibody
FDA-Approved Indication(s):	<p>Indicated for the treatment of Alzheimer’s disease.</p> <ul style="list-style-type: none"> 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. <ul style="list-style-type: none"> ▶ 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). <p>Patient selection: confirm presence of amyloid beta pathology prior to initiating treatment.</p>
How Supplied:	Single-dose vial: 170 mg/1.7 mL (100 mg/mL); 300 mg/3 mL (100 mg/mL).
Dosage and Administration:	<ul style="list-style-type: none"> Titration is required for treatment initiation. Intravenous (IV) infusion every 4 weeks: <ul style="list-style-type: none"> Infusions 1 and 2, dosage is 1 mg/kg; Infusions 3 and 4, dosage is 3 mg/kg; Infusions 5 and 6, dosage is 6 mg/kg; Infusion 7 and beyond, dosage is 10 mg/kg.
Benefit Category:	Medical

Boxed Warning: Amyloid Related Imaging Abnormalities (ARIA)

Monoclonal antibodies directed against aggregated forms of beta amyloid, including Aduhelm[®], can cause 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 (approximately 15% of Alzheimer’s disease patients) treated with this class of medications, including Aduhelm[®], 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 Aduhelm®; however, it cannot be determined if they are ApoE ε4 homozygotes and at higher risk for ARIA.

Consider the benefit of Aduhelm® for the treatment of Alzheimer’s disease and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment with Aduhelm®.

Descriptive Narrative

Alzheimer’s disease (AD) is a fatal neurodegenerative brain disease characterized by the progressive accumulation of beta-amyloid protein plaques and neurofibrillary tangles; these are hypothesized to damage neurons and lead to the loss of cognition and physical functioning. It is the most common cause of dementia among older adults, affecting almost six million people in the United States. Of those, 80% are 75 years of age and older, with more women than men affected and Black Americans at higher risk of developing the disease. Symptoms include impairment of memory, language, executive function, and visuospatial function that affects one’s ability to function. Other symptoms include changes in mood or personality and sleep disturbances. Eventually, patients may require around-the-clock in-home or institutional care. As the disease progresses, caregiving burden – most often done by unpaid family members and friends – increases significantly. Caregivers can suffer significant negative physical, financial, and emotional outcomes from the strain of caregiving.²

Currently approved treatments for treating various stages of dementia associated with AD include:

1. The cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and the N-methyl-D-aspartate (NMDA) receptor antagonist (memantine).
 - These drugs provide modest benefits to patients with AD, but it is unclear if these drugs slow or prevent neurodegeneration in patients with AD.³
2. Aducanumab (Aduhelm®) is a human monoclonal immunoglobulin G1 (IgG1) antibody directed against aggregated soluble and insoluble forms of amyloid beta. The accumulation of amyloid beta plaques in the brain is a defining pathophysiological feature of AD.
 - While it was the first therapy to target the underlying pathophysiology of the disease, Aduhelm® is not a cure and may only slow disease progression.⁴
 - Aduhelm® was approved under the accelerated approval process as a treatment for AD based upon evidence of efficacy from a change in a surrogate endpoint (e.g., amyloid reduction) considered as reasonably likely to predict clinical benefit.
3. Lecanemab-irmb (Leqembi®) is a recombinant humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta.
 - Leqembi® was initially approved under the accelerated approval process as a treatment for AD based upon evidence of efficacy from a change in a surrogate endpoint (e.g., amyloid reduction) considered as reasonably likely to predict clinical benefit.
 - In July 2023, received full FDA approval based on results of the phase 3 trial⁵ that showed a change of 0.45 points on an 18-point scale in the Clinical Dementia Rating – Sum of Boxes (CDR-SB) over 18 months.
 - Leqembi® is also currently under investigation for pre-clinical Alzheimer's disease (clinical trials identifier NCT04468659).⁶

Amyloid Related Imaging Abnormalities (ARIA)

Aduhelm[®] can cause amyloid related imaging abnormalities-edema (ARIA-E), which can be observed on MRI as brain edema or sulcal effusions, and amyloid related imaging abnormalities-hemosiderin deposition (ARIA-H), which includes micro-hemorrhage and superficial siderosis.

The safety of Aduhelm[®] in patients with 10 or more brain microhemorrhages, any pretreatment localized superficial siderosis, and/or with a brain hemorrhage greater than 1 cm within one year of treatment initiation has not been established.

Monitoring for ARIA-E and ARIA-H

- Obtain recent (within one year) baseline brain magnetic resonance imaging (MRI) prior to initiating treatment.
- Obtain brain MRIs 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 (sixth dose of 10 mg/kg) of Aduhelm[®] to evaluate for the presence of asymptomatic ARIA.
- For patients with radiographic findings of ARIA, enhanced clinical vigilance is recommended. Additional MRIs may be considered if clinically indicated.

ARIA-E Management

- Recommendations for dosing in patients with ARIA-E are dependent on clinical symptoms and radiographic severity.
- In Studies 1 and 2, dosing was suspended for symptomatic patients with ARIA-E of any severity and for asymptomatic patients with moderate or severe ARIA-E.
- There is limited experience in patients who continued dosing through symptomatic ARIA-E or through asymptomatic moderate or severe ARIA-E.
- There is limited data in dosing patients who experienced three or more episodes of ARIA-E.
- Use clinical judgment in considering whether to continue dosing in patients with recurrent ARIA-E (more than two episodes).

ARIA-H Management

- Recommendations for dosing in patients with ARIA-H are dependent on the type of ARIA-H and radiographic severity.
- In Studies 1 and 2, dosing was suspended for symptomatic patients with ARIA-H of any severity and for asymptomatic patients with moderate ARIA-H. Dosing was permanently discontinued for any severe ARIA-H.

Guidelines

The American Academy of Neurology (AAN) published guidelines on mild cognitive impairment (MCI) in 2001. A practice guideline update summary was published in January of 2018.⁷ Treatment guidelines do not yet include Aduhelm[®].

In 2022, AAN published the report “Aducanumab Use in Symptomatic Alzheimer’s Disease: Evidence in Focus.” The results of this report included the following statements:
Data were identified from 4 clinical trials, 1 rated Class I and 3 rated Class II.

- The Class I study showed that single doses of aducanumab up to 30 mg/kg were safe and well tolerated.
- All 3 Class II studies provided evidence that aducanumab (3–10 mg/kg) decreased amyloid deposition on brain PET at 1 year vs placebo.
- Efficacy data in the Class II studies varied by dose and outcome, but aducanumab either had no effect on mean change on the Clinical Dementia Rating Sum of Boxes scores or resulted in less worsening (vs placebo) that was of uncertain clinical importance.
- Adverse amyloid-related imaging abnormalities occurred in approximately 40% of individuals treated with aducanumab vs 10% receiving placebo.⁸

Diagnostic Criteria and Rating Scales

Global CDR® Score (CDR-GS)

Calculated score that provides an overall rating of dementia severity using six areas – Memory, Orientation, Judgment/ Problem Solving, Community Affairs, Home/Hobbies, and Personal Care

• 0 = normal • 0.5 = very mild dementia • 1 = mild dementia • 2 = moderate dementia • 3 = severe dementia

Sum of Boxes Score (CDR-SB)

Detailed quantitative general index across the 6 categories.⁹

• 0 = no dementia/normal • 0.5 – 2.0 = questionable impairment • 9.5 – 15.5 = moderate dementia
 • 0.5 – 4.0 = questionable cognitive impairment • 2.5 – 4.0 = very mild dementia • 16.0 – 18.0 = severe dementia
 • 4.5 – 9.0 = mild dementia

Mini Mental State Examination (MMSE)

Tool used to assess cognitive function in older adults. Not used on its own to diagnose dementia but combined with other factors (such as analysis of brain scans, a neurological exam, evaluation of medical history, etc.), it can be used as an indicator of dementia. Scored on a 30-point scale, with items assessing orientation, memory, attention/concentration, language, and visuospatial function.

Advantages of the MMSE are that it is easy to administer, and it only takes about 10 minutes to complete. Disadvantages of the test however include that it requires a certain level of education, which could make it less reliable (i.e., an educated person with dementia may be able to score above a 24, and a person with a sub-eighth grade level of education may score below 24 despite not having dementia, which could lead to a misdiagnosis). The MMSE is also not very sensitive to mild cognitive impairment or early dementia (someone in the beginning stages could still achieve a high score).¹⁰

MMSE Scoring Chart (score range and corresponding level of dementia)	
• 24 and higher = Normal cognition; no dementia	• 10 to 18 = Moderate dementia
• 19 to 23 = Mild dementia	• 9 and lower = Severe dementia

Clinical dementia rating (CDR): The CDR® Dementia Staging Instrument is a 5-point scale. The necessary information to make each rating is obtained through a semi-structured interview of the patient and a reliable informant or collateral source (e.g., family member).¹¹

Clinical dementia rating (CDR): 0, 0.5, 1, 2, 3					
Impairment	None (0)	Questionable (0.5)	Mild (1)	Moderate (2)	Severe (3)
Memory	No memory loss or slight inconstant forgetfulness	Consistent slight forgetfulness; partial recollection of events	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented or slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented in time, often to place	Oriented to person only
Judgment and problem	Solves everyday problems and handles business and financial affairs well; judgment good in relation to past performance	Slight impairment to solving problems, similarities, differences	Moderate difficulty in handling problems, similarities, differences; social judgment usually maintained	Severely impaired in handling problems, similarities, differences; social judgment usually impaired	Unable to make judgments or solve problems
Community affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities though may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside of home; appears well enough to be taken to functions outside of family home	No pretense of independent function outside of home; appears too ill to be taken to functions outside a family home
Home and hobbies	Life at home, hobbies, intellectual interests well maintained	Life at home, hobbies, intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal care	Fully capable of self-care	Fully capable of self-care	Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Criteria

NOTE: Pursuant to the terms of the CMS National Coverage Determination (NCD), Medicare does not cover Aduhelm treatment provided outside of a controlled clinical trial. Medicare-Medicaid dual-eligible members are required to obtain the medication via their Medicare benefit.^{12,13} Medical necessity criteria apply **ONLY** to members who are not dually-eligible (members without Medicare coverage).

Prior authorization is required.

Aduhelm[®] is considered medically necessary when **ALL** of the following are met:

1. Clinical diagnosis of Alzheimer's disease [either mild cognitive impairment (MCI) stage or mild dementia stage]; **AND**
2. Member is 50 to 85 years of age; **AND**
3. Presence of beta-amyloid plaques verified by **AT LEAST ONE** of the following (a or b):
 - a. Positron emission tomography (PET) scan; **AND/OR**
 - b. Cerebrospinal fluid (CSF) testing; **AND**
4. Documented brain magnetic resonance imaging (MRI) within the past 12 months demonstrating **ALL** of the following:
 - a. No localized superficial siderosis; **AND**
 - b. Less than ten (10) brain microhemorrhages; **AND**
 - c. No brain hemorrhages that are > 1 cm in the past year; **AND**
5. Objective evidence of cognitive impairment at screening; **AND**
6. Member meets **ALL** of the following:
 - a. Clinical Dementia Rating Global Score (CDR-GS) of 0.5; **AND**
 - b. Mini-Mental State Examination (MMSE) score ≥ 24 ; **AND**
 - c. Is not taking any blood thinners, except for aspirin ≤ 325 mg; **AND**
 - d. No brain hemorrhage, bleeding disorder, or cerebrovascular abnormalities in the last 6 months; **AND**
7. Other known causes of dementia have been ruled out (e.g., vascular dementia, Parkinson's disease dementia, Lewy body dementia, frontotemporal dementia); **AND**
8. Aduhelm[®] is not used in combination with other therapies directed at amyloid beta (e.g., lecanemab-irmb); **AND**
9. Prescribed by, or in consultation with, a neurologist, geriatrician, or geriatric psychiatrist; **AND**
10. Member does not have dual coverage with Medicare (see above); **AND**
11. Dose does not exceed the following (titration is required for treatment initiation):
 - Intravenous (IV) infusion every 4 weeks.
 - Infusions 1 and 2, dosage is 1 mg/kg;
 - Infusions 3 and 4, dosage is 3 mg/kg;
 - Infusions 5 and 6, dosage is 6 mg/kg;
 - Infusion 7 and beyond, dosage is 10 mg/kg.

NOTE: Pursuant to the terms of the CMS National Coverage Determination (NCD), Medicare does not cover Aduhelm treatment provided outside of a controlled clinical trial. Medicare-Medicaid dual-eligible members are required to obtain the medication via their Medicare benefit.^{10,11} Medical necessity criteria apply **ONLY** to members who are not dually-eligible (members without Medicare coverage).

Aduhelm[®] is considered medically necessary for continuation of therapy when **ALL** of the following are met:

1. Member is currently receiving medication through the Iowa Medicaid benefit or has previously met initial approval criteria; **AND**
2. Member is 50 to 85 years of age; **AND**
3. Member is responding positively to therapy as evidenced by slowed decline in cognition (as assessed by the prescribing provider); **AND**
4. Prior to the 7th and 12th infusions, documentation of recent (within the last month) brain magnetic resonance imaging (MRI) showing **AT LEAST ONE** of the following:
 - a. Less than 10 new incident microhemorrhages and less than 1 focal areas of superficial siderosis; **AND/OR**
 - b. Radiographic stabilization since baseline; i.e., no increase in size or number of amyloid related imaging abnormalities-hemosiderin deposition (ARIA-H); **AND**
5. Aduhelm[®] is not used in combination with other therapies directed at amyloid beta (e.g., lecanemab-irmb); **AND**
6. Prescribed by, or in consultation with, a neurologist, geriatrician, or geriatric psychiatrist; **AND**
7. Member does not have dual coverage with Medicare (see above); **AND**
8. Dose does not exceed 10 mg/kg every 4 weeks (after initial titration period). Supporting clinical documentation must be provided with any request for which the regimen prescribed does not align with FDA-approved labeling.

Approval Duration and Quantity Limits

Authorization Duration:

- Initial authorization: 6 months (6 doses of infusion only)
- Subsequent authorizations:
 - Members with < 7 total infusions: up to the 6th total infusion.
 - Members with < 12 infusions but > 7 infusions: up to the 11th total infusion.
 - Members with > 12 infusions: 6 infusions per prior authorization approval.

Quantity Limits:

- Based on member body weight and the FDA-approved dosing schedule shown as follows:

Infusion #	Dosage	Frequency
Infusions 1 and 2	1 mg/kg per infusion	IV infusion every 4 weeks
Infusions 3 and 4	3 mg/kg per infusion	
Infusions 5 and 6	6 mg/kg per infusion	
Infusion 7 and beyond	10 mg/kg per infusion	

Coding and Product Information

The following list(s) of codes and product information are provided for reference purposes only and may not be all inclusive. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment, nor does the exclusion of a code imply that its association to the HCPCS code is inappropriate.

HCPCS	Description
J0172	Injection, aducanumab-avwa, 2 mg

ICD-10	Description
G30	Alzheimer's disease
G30.0	Alzheimer's disease with early onset
G30.1	Alzheimer's disease with late onset
G30.8	Other Alzheimer's disease
G30.9	Alzheimer's disease, unspecified

NDC	Labeler	Dosage	Pkg Size	Pkg Qty	Units/Pkg
64406-0101-01 (170 mg/1.7 mL)	Biogen, Inc. (64406)	2 mg	1	EA	85
64406-0102-02 (300 mg/3 mL)	Biogen, Inc. (64406)	2 mg	1	EA	150

Compliance

1. Should conflict exist between this policy and applicable statute, the applicable statute shall supersede.
2. Federal and State law, as well as contract language, including definitions and specific contract provisions or exclusions, take precedence over medical policy and must be considered first in determining eligibility for coverage.
3. Medical technology is constantly evolving, and Iowa Medicaid reserves the right to review and update medical policy on an annual or as-needed basis.

Medical necessity guidelines have been developed for determining coverage for member benefits and are published to provide a better understanding of the basis upon which coverage decisions are made. Medical necessity guidelines are developed for selected physician administered medications found to be safe and proven to be effective in a limited, defined population or clinical circumstances. They include concise clinical coverage criteria based on current literature review, consultation with practicing physicians in the service area who are medical experts in the particular field, FDA and other government agency policies, and standards adopted by national accreditation organizations. Criteria are revised and updated annually, or more frequently if new evidence becomes available that suggests needed revisions.

References

¹ Aduhelm prescribing information (08/2023). Biogen Inc.: Cambridge, MA. Available online at www.aduhelmhcp.com. Accessed October 2, 2023.

² Lin GA, Whittington MD, Synnott PG, McKenna A, Campbell J, Pearson SD, Rind DM. Aducanumab for Alzheimer’s Disease: Effectiveness and Value; Final Evidence Report and Meeting Summary. Institute for Clinical and Economic Review, August 5, 2021. Available online at icer.org/assessment/alzheimers-disease-2021/. Accessed July 29, 2022.

³ BLA 761178. U.S. Food and Drug Administration: Office of Neurology’s Summary Review Memorandum on BLA 761178, aducanumab-avwa. Available online at www.accessdata.fda.gov. Accessed January 11, 2022.

⁴ FDA News Release. FDA Grants Accelerated Approval for Alzheimer’s Drug. Available online at www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-drug. Posted June 7, 2021. Accessed January 12, 2022.

⁵ A Study to Confirm Safety and Efficacy of Lecanemab in Participants with Early Alzheimer’s Disease (Clarity AD). ClinicalTrials.gov identifier: NCT03887455. Updated June 12, 2023. www.clinicaltrials.gov/study/NCT03887455. Accessed October 2, 2023.

⁶ AHEAD 3-45 Study: A Study to Evaluate Efficacy and Safety of Treatment with Lecanemab in Participants with Preclinical Alzheimer's Disease and Elevated Amyloid and Also in Participants With Early Preclinical Alzheimer's Disease and Intermediate Amyloid. ClinicalTrials.gov identifier: NCT04468659. Updated June 28, 2023. www.clinicaltrials.gov/study/NCT04468659. Accessed October 2, 2023.

⁷ Petersen RC, Lopez O, Armstrong MJ, Getchius TSD, Ganguli M, Gloss D, Gronseth GS, Marson D, Pringsheim T, Day GS, Sager M, Stevens J, Rae-Grant A. Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018 Jan 16;90(3):126-135. PMID: 29282327.

⁸ Day GS, Scarmeas N, et al. Aducanumab Use in Symptomatic Alzheimer Disease Evidence in Focus: A Report of the AAN Guidelines Subcommittee. *Neurology*. 2022 Apr 12;98(15):619-631. Epub 2022 Feb 23. PMID: 35197360.

⁹ Lynch CA, Walsh C, et al. The clinical dementia rating sum of box score in mild dementia. *Dement Geriatr Cogn Disord*. 2006;21(1):40-3. Epub 2005 Oct 25. PMID: 16254429.



¹⁰ Mendez MF. Mental status scales to evaluate cognition. Wilterdink JL, ed. UpToDate. Waltham, MA: UpToDate Inc. www.uptodate.com. Accessed July 6, 2022.

¹¹ Clinical dementia rating (CDR): Current version and scoring rules. UpToDate. Waltham, MA: UpToDate, Inc. www.uptodate.com. Accessed May 11, 2022.

¹² Centers for Medicare and Medicaid Services. Decision Memo: *Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer’s Disease (CAG-00460N)*. Published April 7, 2022. Available online at www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=305

¹³ Medicaid and CHIP Payment and Access Commission (MACPAC). *Medicaid Coverage of Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer’s Disease*. Presentation given September 15, 2022 at MACPAC meeting. Available online at www.macpac.gov/wp-content/uploads/2022/09/07_Medicaid-Coverage-of-Monoclonal-Antibodies-Directed-Against-Amyloid-for-the-Treatment-of-Alzheimers-Disease-Chris.pdf

Development of utilization management criteria may also involve research into other state Medicaid programs, other payer policies, consultation with experts and review by the Medicaid Clinical Advisory Committee (CAC). These sources may not be referenced individually unless they are specifically published and are otherwise applicable to the criteria at issue.

Criteria Change History			
Change Date	Changed By	Description of Change	Version
	CAC		
Signature			
Change Date	Changed By	Description of Change	Version
10/20/2023	CAC	Annual review. Added information regarding FDA-approval of Leqembi®. Added “Sum of Boxes (CDR-SB) to Diagnostic Criteria and Rating Scales section. Updated guidelines to include reference to “Evidence of Use” report published by the American Academy of Neurology. Added criterion “Not to be used in combination with other anti-amyloid therapies.”	2
Signature			
William (Bill) Jagiello, DO			
Change Date	Changed By	Description of Change	Version
10/21/2022	CAC	Criteria implementation.	1
Signature			
William (Bill) Jagiello, DO			

CAC = Medicaid Clinical Advisory Committee