Aduhelm (aducanumab-avwa)
PAM-042

Iowa Medicaid Program	Prior Authorization	**Effective Date**	01/01/2022
Revision Number	3	**Last Reviewed**	10/18/2024
Reviewed By	Medicaid Medical Director	**Next Review**	10/17/2025
Approved By	Medicaid Clinical Advisory Committee	**Approved Date**	10/21/2022

NOTICE: Biogen, the manufacturer of Aduhelm®, announced that it has discontinued the commercialization and development of Aduhelm®. Patients currently prescribed and taking Aduhelm® are eligible for continued dosing until November 1, 2024. Aduhelm® will no longer be available for purchase after November 1, 2024.

Overview

Medication:[1]	aducanumab-avwa
Brand Name:	Aduhelm®
Pharmacologic Category:	Antidementia agent; amyloid beta-directed antibody
FDA-Approved Indication(s):	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. ▶ 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). Patient selection: confirm presence of amyloid beta pathology prior to initiating treatment.
How Supplied:	Single-dose vial: 170 mg/1.7 mL (100 mg/mL); 300 mg/3 mL (100 mg/mL)
Dosage and Administration:	• 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
Benefit Category:	Medical

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.

Descriptive Narrative

Alzheimer's disease (AD), a neurocognitive disorder, causes progressive cognitive deterioration and is characterized by beta-amyloid deposits and neurofibrillary tangles in the cerebral cortex and subcortical gray matter. Diagnosis is clinical; laboratory and imaging tests are usually done to look for specific findings that suggest Alzheimer's disease and to identify other treatable causes of dementia.

AD is the most common cause of dementia, accounting for 60 to 80 percent of dementias in older people. An estimated 6.7 million Americans aged 65 and older are living with Alzheimer's dementia today, and Alzheimer's disease remains the fifth-leading cause of death in the U.S.[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 modestly improve cognitive function and memory in some patients.
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.
   - Biogen, the manufacturer of Aduhelm®, announced in early 2024 that company resources allocated to Aduhelm® were being reprioritized to advance Leqembi® and to develop new treatment modalities. As a result, **Aduhelm® will no longer be available after November 1, 2024**.[3]

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 trial[4] 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).[5]
4. Kisunla™ (donanemab-azbt) is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against insoluble N-truncated pyroglutamate amyloid beta.
   - Kisunla™ was approved by the FDA on July 2, 2024 (regular approval). It is the first and only amyloid plaque targeting-therapy with evidence to support stopping therapy when amyloid plaques are removed.
   - Lilly is currently recruiting study participants for a clinical trial evaluating Kisunla™ in early symptomatic Alzheimer's disease (clinical trials identifier NCT05508789).[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.
- 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.

ApoE ε4 Carrier Status and Risk of ARIA

Approximately 15% of Alzheimer's disease patients are ApoE ε4 homozygotes. The risk of ARIA, including symptomatic and serious ARIA, is increased in ApoE ε4 homozygotes. Testing for ApoE ε4 status should be performed prior to initiation of treatment with Leqembi® 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.

An FDA-authorized test for detection of ApoE ε4 alleles to identify patients at risk of ARIA if treated with Aduhelm® is not currently available. Currently available tests used to identify ApoE ε4 alleles may vary in accuracy and design.

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] Practice guidelines do not yet include anti-amyloid therapies such as Aduhelm® and will need to be updated to integrate these new therapies and treatment modalities.

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	0.5	1	2	3
normal	very mild dementia	mild dementia	moderate dementia	severe dementia

Sum of Boxes Score (CDR-SB): Detailed quantitative general index across the 6 categories.[8]

- 0 = no dementia/normal
- 0.5 – 4.0 = questionable cognitive impairment
  - 0.5 – 2.5 = questionable impairment
  - 3.0 – 4.0 = very mild dementia
- 4.5 – 9.0 = mild dementia
- 9.5 – 15.5 = moderate dementia
- 16.0 – 18.0 = severe dementia

Mini Mental State Examination (MMSE): A tool used to assess cognitive function in older adults. It is 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. It is scored on a 30-point scale, with items that assess 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).[9]

MMSE Scoring Chart (score range and corresponding level of dementia)

- 24 and higher = Normal cognition; no dementia
- 19 to 23 = Mild dementia
- 10 to 18 = Moderate 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).[10]

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.[11,12] 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.
    - No authorization may be granted beyond November 1, 2024.

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 (and strength)	Labeler (and code)	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 the 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 July 1, 2024.

[2] 2023 Alzheimer's Disease Facts and Figures. Alzheimers Dement. 2023 Apr;19(4):1598-1695. PMID 36918389.

[3] Press Release: Biogen to Realign Resources for Alzheimer's Disease Franchise. January 31, 2024. Available online: investors.biogen.com/news-releases/news-release-details/biogen-realign-resources-alzheimers-disease-franchise.

[4] 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.

[5] 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.

[6] A Study of Donanemab (LY3002813) in Participants With Early Symptomatic Alzheimer's Disease (TRAILBLAZER-ALZ 5). ClinicalTrials.gov identifier: NCT05508789. Updated June 18, 2024. www.clinicaltrials.gov/study/NCT05508789. Accessed July 12, 2024.

[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] 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.

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

[11] 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.

[12] 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
[mm/dd/yyyy]	CAC		[#]
Signature			

Change Date	Changed By	Description of Change	Version
10/18/2024	CAC	Annual review. Added information regarding recently approved Kisunla™. Added language prior to Overview table indicating that Biogen has announced they are discontinuing Aduhelm®; product will not be available after November 1, 2024. Policy will be brought back to January 2025 meeting to be archived.	3
Signature William (Bill) Jagiello, DO			
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 t 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