STATE OF IOWA DEPARTMENT OF
Health AND Human
SERVICES

Leqembi (lecanemab-irmb)
PAM–063

Iowa Medicaid Program:	Prior Authorization	**Effective Date:**	07/06/2023
Revision Number:	1	**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:**	10/20/2023

Overview

Medication:[1]	lecanemab-irmb
Brand Name:	Leqembi®
Pharmacologic Category:	recombinant humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody
FDA-Approved Indication(s):	Indicated for the treatment of Alzheimer's disease. • Treatment with Leqembi® 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. Patient selection: confirm presence of amyloid beta pathology prior to initiating treatment.
How Supplied:	Single-dose vial, available as either 200 mg/2 mL or 500 mg/5 mL
Dosage and Administration:	10 mg/kg once every 2 weeks
Benefit Category:	Medical

Boxed Warning: Amyloid Related Imaging Abnormalities (ARIA)

Monoclonal antibodies directed against aggregated forms of beta amyloid, including Leqembi®, 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 Leqembi®, 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 Leqembi®; however, it cannot be determined if they are ApoE ε4 homozygotes and at higher risk for ARIA.

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

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 trial[5] 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 (as a note: clinical meaningfulness of this change is still unclear since a minimum change of 1 point on the CDR-SB scale is considered clinically significant).
    - Leqembi® is also currently under investigation for pre-clinical Alzheimer's disease (clinical trials identifier NCT04468659).[6]

Amyloid Related Imaging Abnormalities (ARIA)

Leqembi® can cause amyloid related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E), which can be observed on MRI as brain edema or sulcal effusions, and ARIA with hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis. ARIA can occur spontaneously in patients with Alzheimer's disease. ARIA-H associated with monoclonal antibodies directed against aggregated forms of beta amyloid generally occurs in association with an occurrence of ARIA-E. ARIA-H of any cause and ARIA-E can occur together.

The safety of Leqembi® in patients with 4 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, 7th, and 14th infusions. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including an MRI if indicated.

ARIA-E Management

- Recommendations for dosing in patients with ARIA-E depend on clinical symptoms and radiographic severity. Use clinical judgment in considering whether to continue dosing in patients with recurrent ARIA-E.
- There is no experience in patients who continued dosing through symptomatic ARIA-E, or through asymptomatic but radiographically severe ARIA-E.
- There is limited experience in patients who continued dosing through asymptomatic but radiographically mild to moderate ARIA-E.
- There are limited data in dosing patients who experienced recurrent ARIA-E.

ARIA-H Management

- Recommendations for dosing in patients with ARIA-H depend on the type of ARIA-H and radiographic severity.

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 Leqembi®.

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.[8]

- 0 = no dementia/normal
- 0.5 – 4.0 = questionable cognitive impairment
- 0.5 – 2.0 = questionable impairment
- 2.5 – 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:
1) Monoclonal antibodies directed against amyloid that are approved for the treatment of Alzheimer's disease (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 may be covered in a randomized clinical trial under an investigational new drug (IND) application.
2) Monoclonal antibodies directed against amyloid that are approved for the treatment of AD b*ased upon evidence of efficacy from a direct measure of clinical benefit* (such as Leqembi®) may be covered in CMS approved prospective comparative studies. Study data for CMS approved prospective comparative studies may be collected in a registry.[11]

Prior authorization is required.

Leqembi® 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 90 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. Fewer than four brain microhemorrhages (≤ 10 mm at greatest diameter); **AND**
    c. No brain macrohemorrhages (> 10 mm at greatest diameter); **AND**
    d. No evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; **AND**
5. Member has no history of transient ischemic attacks (TIA), stroke, or seizures within the past 12 months; **AND**
6. Objective evidence of cognitive impairment at screening; **AND**
7. Documentation of one of the following baseline cognitive tests (a or b):
    a. Mini-Mental State Examination (MMSE) score ≥ 22; or
    b. Global Clinical Dementia Rating (CDR) score of 0.5 to 1; **AND**
8. Other known causes of dementia have been ruled out (e.g., vascular dementia, Parkinson's disease dementia, Lewy body dementia, frontotemporal dementia); **AND**
9. Leqembi® is not used in combination with other therapies directed at amyloid beta (e.g., aducanumab-avwa); **AND**
10. Prescribed by, or in consultation with, a neurologist, geriatrician, or geriatric psychiatrist; **AND**
11. Dose does not exceed 10 mg/kg every 2 weeks. Supporting clinical documentation must be provided with any request for which the regimen prescribed does not align with FDA-approved labeling.

NOTE: Pursuant to the terms of the CMS National Coverage Determination:
1) Monoclonal antibodies directed against amyloid that are approved for the treatment of Alzheimer's disease (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 may be covered in a randomized clinical trial under an investigational new drug (IND) application.
2) Monoclonal antibodies directed against amyloid that are approved for the treatment of AD b*ased upon evidence of efficacy from a direct measure of clinical benefit* (such as Leqembi®) may be covered in CMS approved prospective comparative studies. Study data for CMS approved prospective comparative studies may be collected in a registry.

Leqembi® 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 90 years of age; **AND**
3. Member is responding positively to therapy as evidenced by improvement OR stabilization in baseline cognitive scoring (as assessed by the prescribing provider); **AND**
4. Prior to the 5th, 7th, and 14th infusions, documentation of recent (within the last month) brain magnetic resonance imaging (MRI) showing radiographic stability:
    a. If 10 or more new incident microhemorrhages or > 2 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 demonstrates radiographic stabilization (i.e., no increase in size or number of ARIA-H); **AND**
5. Leqembi® 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. If request is for a dose increase, new dose does not exceed 10 mg/kg once every 2 weeks. 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: up to 4 months (not to exceed 6 total infusions).*
- Subsequent authorizations:
    - Members with < 7 infusions: up to the 6th total infusion.
    - Members with < 14 but > 7 infusions: up to the 13th total infusion.
    - Members with ≥ 14 infusions: 6 months (up to 13 doses per authorization approval).

* Although ARIA can occur at any time and patients can have more than 1 episode, the majority of ARIA-E radiographic events occurred early in treatment (within the first 7 doses).

Quantity Limits:

- 10 mg/kg every 2 weeks

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
J0174	Injection, lecanemab-irmb, 1 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
62856-0212-01	Eisai Inc. (62856)	1 mg	1	EA	200
62856-0215-01	Eisai Inc. (62856)	1 mg	1	EA	500

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] Leqembi® prescribing information (07/2023). Eisai Inc.: Nutley, NJ. Available online at: www.leqembihcp.com. Accessed August 22, 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] 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.

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

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

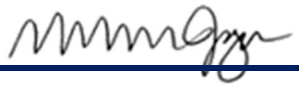
[11] CMS QualityNet. Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease CED Study Registry. Available online at qualitynet.cms.gov/alzheimers-ced-registry. Accessed October 4, 2023.

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
	CAC		
Signature			

Change Date	Changed By	Description of Change	Version
10/20/2023	CAC	Criteria implementation.	1
Signature William (Bill) Jagiello, DO			

CAC = Medicaid Clinical Advisory Committee