Leqembi (lecanemab-irmb)
PAM – 063

Iowa Medicaid Program	Prior Authorization	**Effective Date**	07/06/2023
Revision Number	2	**Last Reviewed**	10/18/2024
Reviewed By	Medicaid Medical Director	**Next Review**	10/17/2025
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, either 200 mg/2 mL or 500 mg/5 mL
Dosage and Administration:	10 mg/kg once every 2 weeks
Benefit Category:	Medical

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 ε 4 Homozygotes

Patients who are apolipoprotein E ε 4 (ApoE ε 4) 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 ε 4 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

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treated with Leqembi®; however, it cannot be determined if they are ApoE ε 4 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.

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.
   - 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, Leqembi® received full FDA approval based on results of the phase 3 trial 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.[4]
    - 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 AD (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)

Leqembi® can cause amyloid related imaging abnormalities –edema (ARIA-E) and –hemosiderin deposition (ARIA-H). 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 majority of ARIA-E radiographic events occurred early in treatment (within the first 7 doses), although ARIA can occur at any time and patients can have more than 1 episode.

Monitoring for ARIA-E and ARIA-H

- Obtain recent (within one year) baseline brain magnetic resonance imaging (MRI) prior to initiating treatment with Leqembi®.
- 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 interruptions in patients with ARIA-E depend on both clinical symptoms and radiographic severity.

- Review prescribing information for dosing interruption recommendations, and use clinical judgment in considering whether to continue dosing in patients with recurrent ARIA-E.

ARIA-H Management

- Recommendations for dosing in patients with ARIA-H depend on both the type of ARIA-H and radiographic severity.
- Review prescribing information for dosing interruption recommendations, and use clinical judgment in considering whether to continue dosing in patients with ARIA-H.

In patients who develop intracerebral hemorrhage greater than 1 centimeter (cm) in diameter during treatment with Leqembi®, suspend dosing until MRI demonstrates radiographic stabilization and symptoms, if present, resolve. Use clinical judgment in considering whether to continue treatment after radiographic stabilization and resolution of symptoms or permanently discontinue Leqembi®.

ApoE ε4 Carrier Status and Risk of ARIA

Approximately 15 percent 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 Leqembi® 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. Practice guidelines do not yet include anti-amyloid therapies such as Leqembi® 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.[7]

- 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). [8]

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): 0, 0.5, 1, 2, 3					
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). [9]					
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® and Kisunla™) may be covered in CMS approved prospective comparative studies. Study data for CMS approved prospective comparative studies may be collected in a registry.[10]

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 demonstrates **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., Aduhelm®, Kisunla™); **AND**
10. Prescribed by, or in consultation with, a neurologist, geriatrician, or geriatric psychiatrist; **AND**
11. Request meets one of the following (a or b):
    a. Regimen prescribed does not exceed 10 mg/kg every 2 weeks; or
    b. Regimen is supported by clinical practice guidelines. Supporting clinical documentation must be provided with any request for which 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® and Kisunla™) may be covered in CMS approved prospective comparative studies. Study data for CMS approved prospective comparative studies may be collected in a registry.[11]

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., Aduhelm®, Kisunla™); **AND**
6. Prescribed by, or in consultation with, a neurologist, geriatrician, or geriatric psychiatrist; **AND**
7. Request meets one of the following (a or b):
    a. Regimen prescribed does not exceed 10 mg/kg every 2 weeks; or
    b. Regimen is supported by clinical practice guidelines. Supporting clinical documentation must be provided with any request for which 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 4 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: 12 months

*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 (Strength)	Labeler	Dosage	Pkg Size	Pkg Qty	Units/ Pkg
62856-0212-01 (200 mg/2 mL)	Eisai Inc. (62856)	1 mg	1	EA	200
62856-0215-01 (500 mg/5 mL)	Eisai Inc. (62856)	1 mg	1	EA	500

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] Leqembi® prescribing information (07/2023). Eisai Inc.: Nutley, NJ. Available online: www.leqembihcp.com. Accessed July 3, 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. www.clinicaltrials.gov/study/NCT03887455. Updated July 9, 2024. Accessed July 12, 2024.

[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 July 9, 2024. www.clinicaltrials.gov/study/NCT04468659. Accessed July 12, 2024.

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

[7] 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.

[8] Mendez MF. Mental status scales to evaluate cognition. Wilterdink JL, ed. UpToDate. Waltham, MA: UpToDate Inc. www.uptodate.com. Accessed July 12, 2024.

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

[10] MLN Matters Number MM13598. National Coverage Determination 200.3: Monoclonal Antibodies for the Treatment of Alzheimer's Disease. Implementation Date: June 24, 2024. Available online at: www.cms.gov/files/document/mm13598-national-coverage-determination-2003-monoclonal-antibodies-treatment-alzheimers-disease.pdf. Accessed July 12, 2024.

[11] MLN Matters Number MM13598. National Coverage Determination 200.3: Monoclonal Antibodies for the Treatment of Alzheimer's Disease. Implementation Date: June 24, 2024. Available online at: www.cms.gov/files/document/mm13598-national-coverage-determination-2003-monoclonal-antibodies-treatment-alzheimers-disease.pdf. Accessed July 12, 2024.

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

Change Date	Changed By	Description of Change	Version
10/18/2024	CAC	Annual review. Descriptive Narrative: added information regarding discontinuation of Aduhelm® on November 1, 2024; also added information on recently approved treatment option Kisunla™. Added section on ApoE ε4 carrier status and risk of ARIA. Changed duration of maintenance authorization (≥ 14 infusions) to 12 months to align with Kisunla™ authorization allowance.	2
Signature William (Bill) Jagiello, DO			
Change Date	**Changed By**	**Description of Change**	**Version**
[mm/dd/yyyy]	CAC	Criteria implementation.	1
Signature William (Bill) Jagiello, DO			

CAC = Medicaid Clinical Advisory Committee