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

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

POLICY

This policy addresses the coverage of Leqembi (lecanemab-irmb) in the treatment of treatment of Alzheimer's disease, specifically, according to the labeled indication, "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."

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

APPLICABLE HCPCS

J0174: Injection, lecanemab-irmb, 1mg; 1 billable unit = 1 mg (Effective 07/06/2023)

Available Dosage Form: 200 mg/2 mL, 500 mg/5 mL solution

CLINICAL CRITERIA

A. INITIAL CRITERIA

Leqembi (lecanemab-irmb) may be authorized when the requirements outlined in CMS National Coverage Determination 200.3 'Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (AD)' (published April 7, 2022) **AND ALL** of the following criteria are submitted with relevant clinical documentation:

1. Prescribed by, or in consultation with, a geriatrician, neurologist, or neuropsychiatrist; **AND**

AND

2. Documented diagnosis of **ONE** of the following (van Dyck 2022):

    a. Mild cognitive impairment (MCI) due to AD; **or**

    b. Mild AD dementia.

AND

3. Baseline disease severity has been assessed utilizing an objective measure/tool AND confirms there is no evidence of moderate or severe AD as documented by the following:

    a. Prescriber has assessed baseline disease severity indicating mild cognitive impairment (MCI) due to AD or mild AD dementia utilizing an objective measure/tool (i.e., Mini-Mental Status Exam [MMSE], Clinical Dementia Rating (CDR), Alzheimer's Disease Assessment Scale-Cognitive Subscale [ADAS-Cog-13], Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory-Mild Cognitive Impairment version [ADCS-ADL-MCI], Clinical Dementia Rating Sum of Boxes [CDR-SB], etc.); **and**

    b. Positron Emission Tomography (PET) scan or CSF assessment is positive for the presence of abnormal amyloid beta plaque burden (van Dyck 2022).

AND

4. Baseline brain MRI prior to initiating treatment and periodically throughout therapy (prescribing information for schedule of MRI scans); **AND**

5. MRI will be reviewed by the Prescriber at the following intervals:

    a. Prior to the 5th, 7th, and 14th infusions (Label 2023); **and**

    b. Prior to the next dose if ARIA is suspected (Label 2023).

AND

6. Member has been evaluated/screened for the presence of the following conditions and there is NO evidence of the following disease or conditions:

    a. Clinically significant and unstable psychiatric illness in the past 6 months; **or**

    b. Stroke or transient ischemic attack (TIA) or seizures in the past 12 months; **or**

    c. Individual with active cancer, undergoing chemotherapy, or has other comorbid condition(s) or diagnosis that poses a high risk of mortality within ONE year; **or**

    d. Currently treated with checkpoint inhibitors, plasmapheresis, IVIG, systemic immunosuppressants, or other monoclonal antibody therapies or derivatives; **or**

    e. Risk factors for intracerebral hemorrhage: prior cerebral hemorrhage greater than 1 cm in greatest diameter; more than 4 microhemorrhages on MRI Gradient-Recall Echo (GRE) and Susceptibility-Weighted (SWI); severe white matter disease; or other abnormalities according to the clinical determination of the treating clinician to be associated with significantly elevated risk for intracerebral hemorrhage with treatment.

B. REAUTHORIZATION / CONTINUATION OF THERAPY CRITERIA

Leqembi (lecanemab-irmb) may be authorized for continuation of therapy when initial criteria have been met AND there is documentation of beneficial response from previous course of treatment:

1. Absence of unacceptable toxicity from the drug (e.g., intracerebral macro hemorrhage, etc.); **AND**

2. Member continues to meet the initial therapy criteria (outlined in section A above) AND has **not** progressed to *moderate or severe AD*, documented by evidence of the following:
   a. No symptomatic moderate to severe ARIA-E; **and**
   b. No moderate to severe ARIA-E based on MRI; **and**
   c. No symptomatic ARIA-H; **and**
   d. No moderate to severe ARIA-H based on MRI.

AND

3. MRI will be reviewed by the prescriber prior to the next dose if ARIA is suspected; **AND**

4. Member has received a pre- 5th, 7th, AND 14th infusion MRI for monitoring of ARIA-E and ARIA-H microhemorrhages.

C. EXCLUSIONS

Leqembi (lecanemab-irmb) may not be authorized for the following (NCT03887455):

1. Any medical or neurological condition, other than AD, that might be a contributing cause of the individual's cognitive impairment; OR
2. Contraindications to brain MRI scanning (such as non-MRI compatible pacemaker/defibrillator or other implants); OR
3. Evidence of other clinically significant lesions on brain MRI that indicate another cause of the individual's cognitive impairment; OR
4. Uncontrolled bleeding disorder, including those with a platelet count greater than 1.5; OR
5. History of transient ischemic attacks (TIA), stroke, or seizures within the past year; OR
6. Any uncontrolled immunological disease or immunological disease requiring treatment with immunoglobulins, systemic monoclonal antibodies (or derivatives of monoclonal antibodies), systemic immunosuppressants, or plasmapheresis.

STEP THERAPY

Step therapy criteria do not apply for members who are currently being treated with the requested medications. Step therapy is only applied for members that are new to therapy (have not received the requested drug in the last 365 days.

A. **PREFERRED PRODUCT: No Step Therapy required.**

DOSAGE AND AUTHORIZATION TIMEFRAMES

1. Recommended Dose: 10 mg/kg and administered as an intravenous infusion over approximately one hour, once every two weeks.

2. Quantity
    a. Leqembi 200 mg/2 mL (100 mg/mL) solution in a single-dose vial: 2 vials every 14 days
    b. Leqembi 500 mg/5 mL (100 mg/mL) solution in a single-dose vial: 2 vials every 14 days.

3. Authorization Period
    a. Initial authorization: May be authorized for up to 6 months.
    b. Continuation of treatment authorization: May be authorized for up to 6 months.

DRUG INFORMATION

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

ROUTE OF ADMINISTRATION: Intravenous Infusion

FDA-APPROVED INDICATIONS

Alzheimer disease (AD)**:** Treatment of AD; to be initiated in patients with mild cognitive impairment or mild dementia stage of disease.

COMPENDIAL APPROVED OFF-LABELED USES: None

Off-Label / Investigational Uses: Requests for off-label uses with a paucity of clinical evidence, or uses that are not generally accepted by the medical community (such as professional guidelines or consensus), CMS-recognized compendia, or peer-reviewed literature is considered investigational and will not be authorized due to insufficient evidence of overall therapeutic value of safety and efficacy.

BOXED WARNING

Amyloid-Related Imaging Abnormalities (ARIA)

Monoclonal antibodies directed against aggregated forms of beta amyloid, including lecanemab, 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 AD patients) treated with this class of medications, including lecanemab, 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 lecanemab; however, it cannot be determined if they are ApoE ε4 homozygotes and at higher risk for ARIA.

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

CONTRAINDICATIONS:

Serious hypersensitivity (e.g., anaphylaxis, angioedema) to lecanemab or any component of the formulation.

OTHER CONSIDERATIONS

Monitoring:

- Delayed progression of AD is evidence of efficacy.
- Confirm the presence of amyloid beta pathology prior to initiating treatment.
- Apolipoprotein E epsilon-4 carrier status: When initiating treatment.
- MRI: Obtain a recent (within one year) brain MRI prior to initiating treatment, and then prior to the 5th, 7th, and 14th infusion.
- Signs and symptoms of amyloid related imaging abnormalities: Especially during the first 14 weeks of treatment.
- Signs or symptoms of infusion-related reaction.

Provider-enrolled patient registry:

CMS requires participation in a CMS-facilitated registry as part of coverage requirements for Leqembi.

The Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) has also established a patient registry comprised of information gathered from volunteer providers regarding Leqembi and other treatments for AD (www.alz-net.org).

CLINICAL SUMMARY / APPENDIX

Alzheimer dementia (AD) is a gradual progressive impairment in cognition and memory, that typically affects adults aged ≥ 65 years and interferes with function and daily activities. AD progresses on a continuum categorized by three phases: (1) preclinical AD (2) mild cognitive impairment (MCI) due to AD and (3) Alzheimer's dementia, which is further, classified into mild, moderate, and severe. As the disease progresses, noticeable symptom changes occur in memory, thinking, and behavioral, impacting the patient's ability to perform activities of daily living. Risk factors for late-onset AD include older age, mutations in the apolipoprotein e4 gene (APOE-e4), and family history of AD. Early-onset AD has been linked to several less common genetic mutations.1 No single test is used to diagnose Alzheimer's dementia but rather a variety of assessments, cognitive tests, and biomarkers collectively assist in making the diagnosis.

Leqembi (lecanemab-irmb) is a humanized immunoglobulin gamma 1 monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta, thereby reducing amyloid beta plaques in patients with AD. Lecanemab is the second amyloid beta-directed antibody indicated for the treatment of AD and should only be initiated in patients with mild cognitive impairment or mild dementia stage of disease. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied.

The efficacy of Leqembi (lecanemab-irmb) was evaluated in one Phase IIb study (Study 1) and one Phase III study (CLARITY AD) (Swanson; van Dyck).

- Leqembi was initially FDA approved through an accelerated program based on the reduction of amyloid beta plaques (surrogate endpoint) from the phase 2 trial. Results from Study 1 demonstrated a reduction in amyloid beta plaque, which served as the basis for FDA approval under the accelerated approval pathway. However, the primary and key secondary clinical efficacy endpoints were not met (Swanson 2021).

- On July 6, 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 (van Dyck 2022). Clinical meaningfulness of this change is still unclear since a minimum change of 1 point on the CDR-SB scale is considered clinically significant (Andrews 2019, Cohen 2022).

Additionally, Leqembi is currently under investigation for pre-clinical Alzheimer's disease (NCT04468659). Results are expected in October 2027.

Definitions

Amyloid Related Imaging Abnormalities (ARIA): Abnormalities observed in the brain on magnetic resonance imaging (MRI).

- ARIA with edema (ARIA-E): findings consistent with brain edema or sulcal effusions
- ARIA with hemorrhage (ARIA-H): findings consistent with microhemorrhage and superficial siderosis

Clinical Dementia Rating (CDR) scale: Measure used to stage dementia in the clinical and research setting, comprising of 75 items related to cognition and function.

Global Score (CDR-GS, or plainly, CDR): 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 = no dementia/normal
- 0.5 = questionable cognitive impairment/very mild dementia
- 1 = mild cognitive impairment/mild dementia
- 2 = moderate dementia
- 3 = severe dementia

*CDR Memory (M) Box Score: Considered the primary category within the CDR-GS rating tool. All other categories are secondary. Final CDR-GS score is based on an algorithm with the memory box score playing a significant role in the calculation.

Sum of Boxes Score (CDR-SB): Detailed quantitative general index across the six categories.

- 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

Mild cognitive impairment (MCI) related to AD: Stage categorized by symptoms of memory and/or other thinking problems that are not normal for the individual's age and education, but that usually do not interfere with his or her independence. Sometimes referred to as the symptomatic predementia phase of AD.

Mini Mental State Examination (MMSE): An 11-question tool used to assess mental status that tests five areas of cognitive function – Orientation, Registration, Attention/Calculation, Recall, and Language. Scale is a range from 0 to 30 with 0 being severe dementia and 30 is no dementia.

REFERENCES

Government Agency

Centers for Medicare and Medicaid Services (CMS). Medicare coverage database: National coverage determination (NCD) (search: Leqembi, lecanemab). Available from CMS: Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (AD)

Prescribing Information

Leqembi (lecanemab) [prescribing information]. Nutley, NJ: Eisai Inc; July 2023.

Peer Reviewed Literature, Guidelines

1. NCT03887455. A Study to Confirm Safety and Efficacy of Lecanemab in Participants With Early Alzheimer's Disease (Clarity AD). ClinicalTrials.gov. National Institute of Health. U.S. National Library of Medicine.
2. Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition

of Alzheimer's disease. Alzheimers Dement. 2018;14(4):535-562.
3. Reish NJ, Jamshidi P, Stamm B, et al. Multiple Cerebral Hemorrhages in a Patient Receiving Lecanemab and Treated with t-PA for Stroke. N Engl J Med 2023 January 4. DOI: 10.1056/NEJMc2215148.
4. Swanson CJ, Zhang Y, Dhadda S, et al. A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody. Alzheimers Res Ther. 2021 Apr 17;13(1):80. PMID: 33865446; PMCID: PMC8053280.
5. Van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease (Clarity AD). NEJM. 2023; 388:9-21. DOI: 10.1056/NEJMoa2212948.

IMPORTANT REMINDER

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

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

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

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

POLICY HISTORY

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