Medical Drug Clinical Criteria

Subject:	Leqembi (lecanemab-irmb)		
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Overview

This document addresses the use of Leqembi (lecanemab-irmb), an amyloid beta-directed antibody indicated for the treatment of Alzheimer's disease (AD). Specifically, the label indicates, "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."

Leqembi was initially FDA approved through an accelerated program based on the reduction of amyloid beta plaques (surrogate endpoint) from a phase 2 trial. 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.

Serious safety concerns include amyloid-related imaging abnormalities (ARIA), which can be observed on magnetic resonance imaging (MRI) as brain edema or sulcal effusions (ARIA-E) or brain bleeding as microhemorrhage and superficial siderosis (ARIA-H). These events were the most serious safety issues in clinical trials. Overall incidence of ARIA with Leqembi was 22% compared to 10% in the placebo group. ARIA with hemorrhage (ARIA-H) was more common in those with ApoE4 (a genetic risk factor for developing Alzheimer's disease).

Frequency of ARIA (van Dyck 2022)

	Lecanemab (10 mg/kg) N = 898	**Placebo** N = 897	**Difference**
ARIA (total)	22%	10%	12%
ARIA-H (total)	17%	9%	8%
ApoE ε4 noncarrier	11%	4%	7%
ApoE ε4 carrier (overall)	20%	11%	9%
ApoE ε4 heterozygote	14%	9%	5%
ApoE ε4homozygote	40%	21%	19%
ARIA-H (symptomatic)	0.7%	0.2%	0.5%
ARIA-E	13%	2%	11%
ARIA-E (symptomatic)	3%	0	3%
Concurrent ARIA-E and ARIA-H	8%	1%	7%

Notably, three deaths that may be related to Leqembi have been reported in the phase 3 open-label extension study. All deaths involved stroke-related complications. These case reports have been published online and detailed in the FDA Summary Review for Leqembi (FDA Summary Review 2023, Mast 2022, Piller Nov 2022, Piller Dec 2022, Prillaman 2022, Reish 2023). The phase 3 open-label extension phase is expected to complete in 2027.

In order to address the serious adverse effects concerning ARIA, Leqembi label recommends baseline brain MRI and periodic monitoring with MRI (e.g., prior to the 5th, 7th, 14th doses). Enhanced clinical vigilance for ARIA is recommended during the first 14 weeks of treatment with Leqembi. If an individual experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including MRI if indicated. If ARIA is observed on MRI, careful clinical evaluation should be performed prior to continuing treatment. If radiographically observed ARIA occurs, treatment recommendations are based on type, severity, and presence of symptoms.

Additionally, per the FDA label in the *Other Risk Factors for Intracerebral Hemorrhage* section, it states "patients were excluded from enrollment in Study 2 [phase 3 study] for findings on neuroimaging that indicated an increased risk for intracerebral hemorrhage. These included findings suggestive of cerebral amyloid angiopathy (prior cerebral hemorrhage greater than 1 cm in greatest diameter, more than 4 microhemorrhages, superficial siderosis, vasogenic edema) or other lesions (aneurysm, vascular malformation) that could potentially increase the risk of intracerebral hemorrhage".

"Warnings and Precautions" for Leqembi label states, "*additional caution should be exercised when considering the administration of antithrombotics or a thrombolytic agent (e.g., tissue plasminogen activator) to a patient already being treated with Leqembi*." In the phase 3 study, baseline use of antithrombotic medication (aspirin, other antiplatelets, or anticoagulants) was allowed if the patient was on a stable dose. Patients taking Leqembi with an anticoagulant alone or combined with an antiplatelet medication or aspirin had an incidence of intracerebral hemorrhage of 2.5% (2/79 patients) compared to none in patients who received placebo. Since most exposures to antithrombotics were to aspirin, the manufacturer states that meaningful conclusions of the true risks of exposure are unknown.

The Leqembi label includes boxed warnings for risk of ARIA caused by amyloid beta-directed monoclonal antibodies, including Leqembi, with possible serious and life-threatening events occurring. Furthermore, serious intracerebral hemorrhage greater than 1 cm have occurred in those treated with this class of drugs. The boxed warning includes recommendations to test for ApoE ε4 carrier status prior to drug initiation, as well as discussion with the patient of the risks of ARIA across genotypes and implications of genetic test results, since ApoE ε4 homozygotes have been found to have a higher incidence of ARIA compared to heterozygotes and noncarriers. Risks versus benefits of initiating therapy with Leqembi should be considered due to the serious adverse events associated with ARIA that could occur. Prescribers should also inform patients that if genotyping cannot be done, they can still be treated with Leqembi, although it is not known if they are at higher risk for ARIA since ApoE ε4 status cannot be determined. At the time of publication of these criteria, there are no FDA-authorized tests for the detection of ApoE ε4 alleles to identify at-risk patients. Current available tests may vary in accuracy and design according to the FDA label for Leqembi.

Several voluntary provider-enrolled patient registries have been created to collect real world data so that information can be collected on novel treatments for Alzheimer's disease, including the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET). Providers may obtain information about the ALZ-NET at www.alz-net.org or contact alz-net@acr.org. Of note, the Centers for Medicare and Medicaid Services (CMS) requires participation in their own nationwide, CMS-facilitated registry as part of their coverage requirements for monoclonal antibodies directed against amyoid for the treatment of AD.

On May 16, 2025, the FDA approved the first in vitro diagnostic blood test to aid in diagnosing Alzheimer's disease, the Lumipulse G pTau217/ß-Amyloid 1-42 Plasma Ratio. The new Lumipulse test is approved for the early detection of amyloid plaques associated with Alzheimer's disease in adult patients, aged 55 years and older, exhibiting signs and symptoms of the disease. However, per the FDA press release, "*the Lumipulse G pTau217/ß-Amyloid 1-42 Plasma Ratio is not intended as a screening or stand-alone diagnostic test and other clinical evaluations or additional tests should be used for determining treatment options."* The Alzheimer's Association is leading the development of clinical practice guidelines for the use of blood biomarker tests in specialty care settings, which will be debuted this summer at the Alzheimer's Association International Conference (AAIC), July 27-31. In the meantime, the Association urges providers to refer to the 2022 appropriate use recommendations for blood tests in clinical practice and trial settings which state, "*we recommend to cautiously start using BBMs* [blood biomarkers] *in specialized memory clinics as part of the diagnostic work-up of patients with cognitive symptoms and the results should be confirmed whenever possible with CSF or PET. Additional data are needed before use of BBMs as stand-alone diagnostic AD markers, or before considering use in primary care."*

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.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Leqembi (lecanemab)

Initial requests for Leqembi (lecanemab-irmb) may be approved if the following criteria are met:

I. Leqembi is prescribed by, or in consultation with, a neurologist, geriatrician, neuropsychiatrist, or psychiatrist; **AND**
II. Individual is 50 to 90 years of age (van Dyck 2022); **AND**
III. Individual has a diagnosis of one of the following (van Dyck 2022):
    A. Mild cognitive impairment (MCI) due to Alzheimer's Disease (AD);
    OR
    B. Mild AD dementia;

AND

IV. Documentation is provided that individual has objective impairment in episodic memory according to memory tests [i.e., Free and Cued Selective Reminding Test, the Rey Auditory Verbal Learning Test, the California Verbal Learning Test, or the Logical Memory I and II of the Wechsler Memory Scale Revised (or other versions)] (Albert 2011; van Dyck 2022); **AND**
V. Documentation is provided that individual has a Clinical Dementia Rating (CDR)-Global score of 0.5 to 1.0 (NCT03887455); **AND**
VI. Documentation is provided that individual has a CDR Memory Box score ≥ 0.5 (NCT03887455); **AND**
VII. Documentation is provided that individual has a Mini Mental State Examination (MMSE) score of 22 to 30 (inclusive) (NCT03887455; Perneczky 2006); **AND**

VIII. Documentation is provided that individual has presence of amyloid beta based on one of the following diagnostic tests (van Dyck 2022; Jack 2018):
   A. PET imaging showing presence of amyloid beta;
      OR
   B. Presence of long form amyloid beta (i.e., $A\beta_{1-42}$, Beta-amyloid [1-42], Abeta42) in the cerebrospinal fluid;

AND

IX. Documentation is provided that individual has had a baseline MRI (within the past year) that does ***not*** show any of the following (Label; NCT03887455):
   A. More than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter); **OR**
   B. A single macrohemorrhage >10 mm at the greatest diameter; **OR**
   C. An area of superficial siderosis; **OR**
   D. Evidence of vasogenic edema; **OR**
   E. Evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; **OR**
   F. Evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease; **OR**
   G. Space occupying lesions; **OR**
   H. Brain tumors (except those diagnosed as meningiomas or arachnoid cysts and <1 cm at their greatest diameter);

AND

X. MRI will be reviewed by the prescriber prior to the 5th, 7th, and 14th infusions (Label 2023); **AND**
XI. MRI will be reviewed by the prescriber prior to the next dose if ARIA is suspected (Label 2023); **AND**
XII. The prescriber and individual (or caregiver) have discussed and acknowledged the potential safety risks of treatment, including risks of ARIA-H and ARIA-E (Label 2023); **AND**
XIII. The prescriber and individual have discussed and acknowledged that individuals who are apolipoprotein E (ApoE) ε4 homozygotes (approximately 15% of individuals with AD) treated with Leqembi have a higher incidence of ARIA, including symptomatic, serious, and severe radiographic ARIA compared to heterozygotes and non-carriers (Label 2023).

Continuation requests for Leqembi (lecanemab-irmb) may be approved if the following criteria are met (Label 2023):

I. Individual does *not* have evidence of symptomatic moderate to severe ARIA-E; **AND**
II. Documentation is provided that individual does *not* have evidence of moderate to severe ARIA-E based on MRI; **AND**
III. Individual does *not* have evidence of symptomatic ARIA-H; **AND**
IV. Documentation is provided that individual does *not* have evidence of moderate to severe ARIA-H based on MRI; **AND**
V. MRI will be reviewed by the prescriber prior to the next dose if ARIA is suspected; **AND**
~~V.~~VI. Based on the clinical judgement of the provider, the benefits of continuation outweigh the risks.

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

I. Any medical or neurological condition, other than AD, that might be a contributing cause of the individual's cognitive impairment; **OR**
II. History of transient ischemic attacks (TIA), stroke, or seizures within the past year; **OR**
III. Contraindications to brain MRI scanning (such as non-MRI compatible pacemaker/defibrillator or other implants); **OR**
IV. Evidence of other clinically significant lesions on brain MRI that indicate another cause of the individual's cognitive impairment; **OR**
V. Uncontrolled bleeding disorder, including those with a platelet count <50,000 or international normalized ratio [INR] >1.5; **OR**
VI. Any uncontrolled immunological disease or immunological disease requiring treatment with immunoglobulins, systemic monoclonal antibodies (or derivatives of monoclonal antibodies), systemic immunosuppressants, or plasmapheresis; **OR**
~~VI.~~VII. When the above criteria are not met and for all other indications.

Approval Duration
Initial requests: 4 months
Continuation requests: 6 months

Quantity Limits

Leqembi (lecanemab-irmb) Quantity Limits

Drug	Dosing Limit
Leqembi (lecanemab-irmb) 200 mg/2 mL, 500 mg/5 mL solution	10 mg/kg every 2 weeks

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J0174	Injection, lecanemab-irmb, 1mg [Leqembi]

ICD-10 Diagnosis

G30.0-G30.9	Alzheimer's disease ~~w/early onset~~
~~G30.1~~	~~Alzheimer's disease w/late onset~~
~~G30.8~~	~~Other Alzheimer's disease~~
~~G30.9~~	~~Alzheimer's disease, unspecified~~
~~F06.70-F06.71~~	~~Mild neurocognitive disorder due to known physiological condition~~

Document History

Revised: 08/15/2025
Document History:

- 08/15/2025 – Annual Review: Update continuation criteria to add benefits vs. risks statement. Add statement to non-approvable criteria regarding restrictions for all other indications. Coding Reviewed: Combined ICD-10-CM G30.0-G30.9 into one range and updated description. Removed ICD-10-CM F06.70-F06.71. Updated description for HCPCS J0174.
- 08/16/2024 – Annual Review: No changes. Coding Reviewed: No changes.
- 08/18/2023 – Annual Review: No changes.
- 07/13/2023 – Annual Review: Update clinical criteria for Leqembi and add quantity limits. Effective 7/6/2023 Added HCPCS J0174. Added ICD-10-CM G30.0, G30.1, G30.8, G30.9, F06.70-F06.71. Removed HCPCS J3490, J3590.
- 01/06/2023 – Annual Review: Add new clinical criteria document for Leqembi. Coding Reviewed: Added J3490, J3590. All diagnoses pend.

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Federal and state laws or requirements, contract language, and Plan utilization management programs or policies may take precedence over the application of this clinical criteria.