09-J4000-41

Original Effective Date: 03/15/23

Reviewed: 02/12/25

Revised: 03/15/25

Subject: Lecanemab-irmb (Leqembi) intravenous infusion

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DESCRIPTION:

Alzheimer's disease (AD) is a gradual, progressive dementia that impacts memory and cognition typically in patients 65 years of age and older. Its prevalence is estimated to be 1-2% of patients less than or equal to 65 years and increases with age to approximately 30-50% of patients at 85 years. Risk factors for the development of AD include diabetes, hypertension, dyslipidemia, metabolic syndrome, obesity, smoking, cerebrovascular injury, female sex, family history of AD, and the presence of the epsilon-4 allele of the *APOE* gene. Neurological findings consistent with AD include the presence of neurofibrillary tangles of tau protein and beta-amyloid plaques. AD is a debilitating disease as it eventually impairs the patient's ability to conduct daily activities and causes additional psychological symptoms including, but not limited to, anxiety, depression, confusion, agitation, delusions, and hallucinations. Following diagnosis at 60-69 years of age, the estimated median survival is approximately 6.7 years.

Management of AD is guided by dementia severity. Standard therapeutic options include acetylcholinesterase inhibitors (i.e., donepezil, rivastigmine, galantamine) for all stages of dementia and memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, for moderate-to-severe AD. In June 2021, aducanumab-avwa (Aduhelm), a human, immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against amyloid beta, was FDA approved via the accelerated pathway based on a reduction in amyloid beta plaques in mild AD; however, the agent did not demonstrate any clinical improvement in patients and has limited therapeutic utility outside of ongoing clinical trials.

On January 6, 2023, the FDA approved another human, immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against amyloid beta, lecanemab-irmb (Leqembi), via the accelerated pathway. Lecanemab-irmb was evaluated in two clinical trials: (1) a phase 2 proof-of-concept study and (2) a phase 3 randomized, placebo-controlled study. The phase 2 study was an 18-month, multicenter, double-blind, placebo-controlled clinical trial employing response adaptive randomization across placebo and five lecanemab arms (2.5 mg/kg biweekly, 5 mg/kg monthly, 5 mg/kg biweekly, 10 mg/kg

monthly, 10 mg/kg biweekly) to assess safety and efficacy in subjects with early AD. A total of 854 patients (lecanemab = 609 patients and placebo = 245 patients) were enrolled, and the 10 mg/kg biweekly dosing regimen was identified as the effective dose 90% (ED90), defined as the simplest dose that achieves ≥90% of the maximum treatment effect. The primary endpoint was the clinical change in the Alzheimer's Disease Composite Score (ADCOMS) at 12 months, which was not met. However, lecanemab did reduce brain amyloid on positron emission tomography (PET) at 18 months. Lecanemab was associated with infusion reactions (Grade 1-2) and amyloid-related imaging abnormalities-edema (ARIA-E) with an incidence of 10% at the highest doses for the overall population and 14.3% for apolipoprotein E4 (ApoE4)-positive patients. ARIA-H (new cerebral microhemorrhages, cerebral macrohemorrhages, and superficial siderosis) were reported in 5.3% of placebo patients and 10.7% of lecanemab patients.

Lecanemab was evaluated in an 18-month, phase 3, randomized, double-blind, multicenter clinical trial (Clarity AD). A total of 1,795 patients 50 to 90 years of age with mild cognitive impairment or mild dementia due to AD and with evidence of amyloid on PET or by cerebrospinal fluid testing were assigned to receive either lecanemab 10 mg/kg biweekly (n=898) or placebo (n=897). The primary end point was the change from baseline at 18 months in the score on the Clinical Dementia Rating–Sum of Boxes (CDR-SB; range, 0 to 18, with higher scores indicating greater impairment). The mean CDR-SB score at baseline was approximately 3.2 in both arms. The adjusted least-squares mean change from baseline at 18 months was 1.21 with lecanemab and 1.66 with placebo (difference, −0.45; 95% confidence interval [CI], −0.67 to −0.23; P<0.001). As a secondary endpoint, markers of amyloid, tau, neurodegeneration, and neuroinflammation were reduced to a greater extent with lecanemab than with placebo. Lecanemab was associated with infusion-related reactions (1.2%), ARIA-E (12.6%), and ARIA-H (17.3%). The deaths reported during the blinded portion of the study were not considered related to lecanemab; however, a couple of deaths reported during the open-label extension study are currently under investigation.

On July 6, 2023, the FDA granted traditional approval for lecanemab-irmb (Leqembi) for the treatment of AD patients with mild cognitive impairment (MCI) or mild dementia stage of the disease, which was the population enrolled in the Clarity AD trial. On January 26, 2025, the FDA approved the extended interval dosing regimen of 10 mg/kg intravenously every four weeks for patients completing the initiation phase of 10 mg/kg intravenously every two weeks for 18 months.

POSITION STATEMENT:

Administration of lecanemab-irmb (Leqembi), **meets the definition of medical necessity** when ALL of the following are met:

1. Member is 50 to 90 years of age
2. Diagnosis of mild cognitive impairment (MCI) due to Alzheimer's Disease (AD) or mild AD dementia with "mild disease" documented by all of the following within the last 6 months ("i", "ii", and "iii"): - Documentation must be provided
    i. Clinical Dementia Rating (CDR)-Global Score of 0.5-1.0
    ii. CDR Memory Box Score of at least 0.5
    iii. Mini-Mental Status Exam (MMSE) score between 20-30, inclusive

3. Baseline disease severity has been conducted within the last 6 months using one of the following objective measure tools ("i", "ii", "iii" or "iv"): – Documentation must be provided
    i. Mini-Mental Status Exam (MMSE)
    ii. Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog-13)
    iii. Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory-Mild Cognitive Impairment version (ADCS-ADL-MCI)
    iv. Clinical Dementia Rating-Sum of Boxes [CDR-SB]
4. Positron Emission Tomography (PET) scan or CSF assessment of Aß (1-42) within the last 1 year is positive for amyloid beta plaque – Documentation must be provided
5. Baseline brain magnetic resonance imaging (MRI) obtained within 1 year prior to initiation of treatment with none of the following risk factors for intracerebral hemorrhage present – Documentation must be provided
    i. More than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter)
    ii. A single macrohemorrhage >10 mm at the greatest diameter
    iii. An area of superficial siderosis
    iv. Evidence of vasogenic edema
    v. Evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions
    vi. Evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease
    vii. Space occupying lesions
    viii. Brain tumors (except those diagnosed as meningiomas or arachnoid cysts and <1 cm at their greatest diameter);
6. If concomitantly taking an antithrombotic medication (e.g., aspirin, other antiplatelets, or anticoagulants) the dose has been stable for at least 4 weeks.
7. Member has been informed that those who are apolipoprotein E ε4 (ApoE ε4) homozygotes have a higher incidence of developing ARIA.
8. **NOT** prescribed in combination with donanemab-azbt (Kisunla)
9. The medication is prescribed by a neurologist, neuropsychiatrist, or geriatric specialist with experience in treating dementia
10. The dosage does not exceed 10 mg/kg IV every 14 days

Approval duration: 6 months

Lecanemab-irmb (Leqembi) is considered **experimental or investigational** for any other indications due to insufficient evidence in the peer-reviewed medical literature to support safety, efficacy, and net health outcome.

Continuation of lecanemab-irmb (Leqembi) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Authorization/reauthorization for the requested agent has been previously approved by Florida Blue or another health plan in the past 2 years (if another health plan, documentation of a health plan-paid claim during the 90 days before the authorization request must be submitted), OR the member currently meets all indication-specific initiation criteria.
2. MRIs have been obtained prior to the 5th, 7th, AND 14th infusion for monitoring of Amyloid Related Imaging Abnormalities-edema (ARIA-E) and Amyloid Related Imaging Abnormalities-hemosiderin (ARIA-H) microhemorrhages – Documentation must be provided
3. Member has not experienced any adverse effects such as amyloid related imaging abnormalities-edema (ARIA-E) and -hemosiderin deposition (ARIA-H), intracerebral hemorrhage, or severe hypersensitivity reactions necessitating discontinuation of therapy.
4. Member has not progressed to moderate or severe AD and responded to therapy compared to their pre-treatment baseline as evidenced by improvement, stability, or slowing in cognitive and/or functional impairment (e.g., ADAS-Cog 13; ADCS-ADL-MCI; MMSE; CDR-SB) – Documentation must be provided using the same disease severity tool used at baseline
5. **NOT** prescribed in combination with donanemab-azbt (Kisunla)
6. The medication is prescribed by**,** or in consultation with, a neurologist, neuropsychiatrist, or geriatric specialist with experience in treating dementia
7. The dosage does not exceed 10 mg/kg IV every 14 days

Approval duration: 6 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Lecanemab (Leqembi) is indicated for the treatment of Alzheimer's disease. Treatment with 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.
- The recommended dosage is 10 mg/kg once every 2 weeks via intravenous infusion for 18 months. After 18 months, continue treatment once every 2 weeks or once every 4 weeks.
- Lecanemab (Leqembi) must be diluted in 250 mL of 0.9% Sodium Chloride Injection, USP, prior to administration.
- The infusion should be administered over approximately one hour via a terminal low-protein binding 0.2 micron in-line filter.
- Obtain a recent (within one year) brain MRI prior to initiating treatment to evaluate for pre-existing Amyloid Related Imaging Abnormalities (ARIA) and prior to the 5th, 7th, and 14th

infusions. If radiographically observed ARIA occurs, treatment recommendations are based on type, severity, and presence of symptoms.

Dose Adjustments

Table 1: Dosing Recommendations for Patients with ARIA-E

Clinical Symptom Severity[1]	ARIA-E Severity on MRI		
	Mild	Moderate	Severe
Asymptomatic	May continue dosing	Suspend dosing[2]	Suspend dosing[2]
Mild	May continue dosing based on clinical judgment	Suspend dosing[2]	
Moderate or Severe	Suspend dosing[2]		

1 Mild: discomfort noticed, but no disruption of normal daily activity.
Moderate: discomfort sufficient to reduce or affect normal daily activity.
Severe: incapacitating, with inability to work or to perform normal daily activity.

2. Suspend until MRI demonstrates radiographic resolution and symptoms, if present, resolve; consider a follow-up MRI to assess for resolution 2 to 4 months after initial identification. Resumption of dosing should be guided by clinical judgment.

Table 2: Dosing Recommendations for Patients with ARIA-H

Clinical Symptom Severity'	ARIA-H Severity on MRI		
	Mild	Moderate	Severe
Asymptomatic	May continue dosing	Suspend dosing[1]	Suspend dosing[2]
Symptomatic	Suspend dosing[1]	Suspend dosing[1]	

1. Suspend until MRI demonstrates radiographic stabilization and symptoms, if present, resolve; resumption of dosing should be guided by clinical judgment; consider a follow-up MRI to assess for stabilization 2 to 4 months after initial identification.
2. Suspend until MRI demonstrates radiographic stabilization and symptoms, if present, resolve; use clinical judgment in considering whether to continue treatment or permanently discontinue lecanemab (Leqembi).

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

Drug Availability

- 500 mg/5 mL (100 mg/mL) solution for injection in a single-dose vial
- 200 mg/2 mL (100 mg/mL) solution for injection in a single-dose vial

PRECAUTIONS:

Boxed Warning

- **Amyloid Related Imaging Abnormalities**: Monoclonal antibodies directed against aggregated forms of beta amyloid, including lecanemab (Leqembi), can cause amyloid related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E) and ARIA with hemosiderin deposition (ARIA-H). ARIA is usually asymptomatic, although rarely serious and life-threatening events can occur. Serious intracerebral hemorrhage greater than 1 cm have occurred in patients treated with this class of medications. ARIA-E can cause focal neurologic deficits that can mimic ischemic stroke.
- **ApoE ε4 Homozygotes**: Patients treated with this class of medications, including lecanemab (Leqembi), who are ApoE ε4 homozygotes have a higher incidence of ARIA, including symptomatic and serious 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.
- Consider the benefit of lecanemab (Leqembi) for the treatment of Alzheimer's disease and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment with lecanemab (Leqembi).

Contraindications

- Lecanemab (Leqembi) is contraindicated in patients with a history of serious hypersensitivity to lecanemab-irmb or to any of the excipients. Hypersensitivity reactions, including angioedema, bronchospasm, and anaphylaxis, have occurred in patients who were treated with lecanemab-irmb. Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction and initiate appropriate therapy.

Precautions/Warnings

- **Amyloid Related Imaging Abnormalities (ARIA):** Enhanced clinical vigilance for ARIA is recommended during the first 14 weeks of treatment with lecanemab (Leqembi). Risk of ARIA, including symptomatic ARIA, was increased in apolipoprotein E ε4 homozygotes compared to heterozygotes and noncarriers. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including MRI scanning if indicated.
- **Infusion-Related Reactions:** Symptoms of infusion-related reactions include fever and flu-like symptoms (chills, generalized aches, feeling shaky, and joint pain), nausea, vomiting, hypotension, hypertension, and oxygen desaturation. The infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy administered as clinically indicated. Consider pre-medication at subsequent dosing with antihistamines, non-steroidal anti-inflammatory drugs, or corticosteroids.
- **Use of Antiplatelet, Anticoagulant, and Antithrombotic Medications:** Caution should be exercised when considering lecanemab (Leqembi) in patients receiving antiplatelets other than aspirin, anticoagulants, and antithrombotic medications (e.g., tissue plasminogen activator). As described in the prescribing information, patients taking anticoagulant medications at baseline were excluded from Study 1. However, antiplatelet medications (i.e., aspirin and clopidogrel)

were allowed. If an anticoagulant medication was used for a patient during Study 1 that required treatment for 4 weeks or less, lecanemab (Leqembi) treatment was temporarily suspended. Patients who received lecanemab (Leqembi) and an antithrombotic medication (aspirin, other antiplatelets, or anticoagulants) did not appear to have an increased risk of ARIA-H compared to patients who received placebo and an antithrombotic medication. The majority of exposures to antithrombotic medications were to aspirin; few patients were exposed to other antiplatelet drugs or anticoagulants, limiting any meaningful conclusions about the risk of ARIA or intracerebral hemorrhage in patients taking other antiplatelet drugs or anticoagulants. Because intracerebral hemorrhages greater than 1 cm in diameter have been observed in patients taking lecanemab (Leqembi), additional caution should be exercised when considering the administration of antithrombotics or a thrombolytic agent.

- **Patients with Risk Factors for Intracerebral Hemorrhage:** Caution should be exercised when considering lecanemab (Leqembi) in patients with the following intracerebral hemorrhage risk factors, as these were exclusion criteria for Study 1 as described in the prescribing information: prior cerebral hemorrhage greater than 1 cm in greatest diameter, more than 4 microhemorrhages, superficial siderosis, evidence of vasogenic edema, evidence of cerebral contusion, aneurysm, vascular malformation, infective lesions, multiple lacunar infarcts or stroke involving a major vascular territory, and 7 severe small vessel or white matter disease.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J0174	Injection, lecanemab-irmb, 1mg

ICD-10 Diagnosis Codes That Support Medical Necessity

G30.0 – G30.9	Alzheimer's disease

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

Section 1: Standard CDR

Please enter scores below.	IMPAIRMENT				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
1. MEMORY	No memory loss, or slight inconsistent forgetfulness.	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness.	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.
2. ORIENTATION	Fully oriented.	Fully oriented except for 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 to time, often to place.	Oriented to person only.
3. JUDGMENT AND PROBLEM SOLVING	Solves everyday problems. Handles business and financial affairs well; judgment good in relation to past performance.	Slight impairment in these activities.	Moderate difficulty in handling problems, similarities and differences; social judgment usually maintained.	Severely impaired in handling problems, similarities and differences; social judgment usually impaired.	Unable to make judgments or solve problems.
4. COMMUNITY AFFAIRS	Independent function at usual level in job. shopping, volunteer and social groups.	Life at home, hobbies and intellectual interests slightly impaired.	Unable to function independently at these activities, although may still be engaged in some; appears normal to casual inspection.	No pretense of independent function outside the home; appears well enough to be taken to functions outside the family home.	No pretense of independent function outside the home; appears too ill to be taken to functions outside the family home.
5. HOME & HOBBIES	Life at home. hobbies and intellectual interests well maintained.	Life at home, hobbies, and 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 the home.
6. PERSONAL 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.

Sum of Boxes Staging Category

CDR Sum of Boxes Range	Staging Category
0	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

RELATED GUIDELINES:

Donanemab-azbt (Kisunla) intravenous infusion, 09-J4000-94

OTHER:

None

REFERENCES:

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 02/12/25.

GUIDELINE UPDATE INFORMATION:

03/15/23	New Medical Coverage Guideline – Lecanemab-irmb (Leqembi) is considered not medically necessary for all indications including, but not limited to, Alzheimer's disease

	(AD), cognitive impairment due to AD, and AD dementia, as a clinical benefit has not been established.
07/18/23	Update HCPCS coding from J3590 to J0174
11/15/23	Review and revision to the guideline consisting of revising the Position Statement, including the new indication and box warning based on the full approval from the FDA, and updating references.
06/15/24	Review and revision to the guideline consisting of revising the Position Statement to include geriatric specialists as prescribers and allow consultation for prescribing on continuation and to clarify that baseline MRIs should be obtained within 1 year prior to initiation of therapy and updating references.
09/15/24	Review and revision to the guideline consisting of revising the Position Statement to specify that baseline assessments should be performed within the last 6 months and to not allow concomitant therapy with donanemab-azbt (Kisunla).
03/15/25	Review and revision to the guideline consisting of revising the Position Statement to extend the range for the MMSE assessment from 22-30 to 20-30 for “mild cognitive impairment” and the baseline assessment for amyloid beta plaque from 6 months to 1 year, updating the new FDA approved extended interval dosing to every 4 weeks after 18 months of the initiation phase, revising precaution and box warning language, and updating references.