Leqembi and Leqembi Iqlk(Lecanemab-irmb)

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This medical policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

FDA-Approved Indications

Leqembi is 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 the clinical trials.

POLICY

Required Documentation

Submission of the following information is necessary to initiate the prior authorization review:

A. Initial Requests:
   1. Genetic testing results documenting a mutation in amyloid precursor protein (*APP*), presenilin-1 (*PSEN1*), or presenilin-2 (*PSEN2*), if applicable.
   2. Clinical documentation to support early onset Alzheimer’s Disease, if applicable.
   3. Medical records (e.g., chart notes) documenting the following:
      i. Diagnosis of mild cognitive impairment due to Alzheimer’s Disease or mild Alzheimer’s Disease.
      ii. Baseline assessments for any of the following assessment tools:
         a. Clinical Dementia Rating-Global Score (CDR-GS)
         b. Mini-Mental Status Examination (MMSE)
         c. Montreal Cognitive Assessment (MoCA)

d. St. Louis University Mental State Exam (SLUMS)

4. Presence of amyloid pathology documented by either of the following:
   i. Baseline positron emission tomography (PET) scan
   ii. Lumbar puncture results
5. Recent (within one year) brain magnetic resonance imaging (MRI) prior to initiating treatment.

B. Continuation requests (where applicable):
1. Medical records (e.g., chart notes) documenting the most recent (less than 1 month prior to continuation request) assessment tool for any of the following:
   i. Clinical Dementia Rating-Global Score (CDR-GS)
   ii. Mini-Mental Status Exam (MMSE)
   iii. Montreal Cognitive Assessment (MoCA)
   iv. St. Louis University Mental State Exam (SLUMS)
2. Brain magnetic resonance imaging (MRI) results prior to the 3rd dose, 5th dose, 7th dose, and 14th dose.

Prescriber Specialties

The requested medication must be prescribed by or in consultation with one of the following:

1. Geriatrician
2. Neurologist
3. Psychiatrist

Criteria for Initial Approval

Authorization of 12 months may be granted for treatment of Alzheimer's Disease (AD) when all of the following criteria are met:

A. Member must meet one of the following criteria:
1. Member is 50 years of age or older
2. If less than 50 years of age, member has a genetic mutation in amyloid precursor protein *(APP)*, presenilin-1 *(PSEN1)*, or presenilin-2 *(PSEN2)*, or other clinical documentation to support early onset AD.

B. Member must have mild cognitive impairment due to AD or mild AD dementia.

C. Member must have objective evidence of cognitive impairment at baseline (Appendix A).

D. Member must have one of the following scores at baseline on any of the following assessment tools:
1. Clinical Dementia Rating-Global Score (CDR-GS) of 0.5 or 1 (Appendix B).
2. Mini-Mental Status Examination (MMSE) score of 21 – 30 (Appendix C).
3. Montreal Cognitive Assessment (MoCA) score of greater than or equal to 16 (Appendix D)
4. St. Louis University Mental State Exam (SLUMS) score of greater than or equal to 16

E. Member must meet one of the following criteria:
1. Have a positron emission tomography (PET) scan confirming the presence of amyloid pathology.
2. Have results from a lumbar puncture confirming at least one of the following detected in cerebrospinal fluid (CSF):
   i. Low AB42/AB40 ratio
   ii. Elevated P-Tau/AB42 ratio
   iii. Elevated T-Tau/AB42 ratio

F. Member must have a recent brain magnetic resonance imaging (MRI) within one year prior to initiating treatment to evaluate for pre-existing Amyloid Related Imaging Abnormalities (ARIA).

G. Member meets one of the following regarding apolipoprotein E ε4 (ApoE ε4) status:
1. Genotype testing for ApoE ε4 status has been performed prior to initiation of treatment to inform member of the risk of developing ARIA.
2. Genotype testing has not been performed and the prescriber has informed the member that it cannot be determined if they are ApoE ε4 homozygous and may be at higher risk for ARIA.

H. If there is concurrent use of antithrombotic medications (aspirin, other antiplatelets, or anticoagulants), the member has been on a stable dose for at least 4 weeks prior to initiation of the requested medication.

Continuation of Therapy

Authorization of 6 months (first reauthorization after the initial 12 month approval period) may be granted for members requesting continuation of therapy when all of the following criteria are met:

A. Member has met all initial authorization criteria at the time of initial approval.
B. Member has been evaluated for evidence of amyloid-related imaging abnormalities (ARIA) on MRI prior to the 3rd dose, 5th dose, 7th dose and 14th dose. (Appendix E).
    1. For members with radiographic evidence of ARIA-E:
        i. Dosing may continue based on clinical judgement, if applicable, for members that meet the following criteria:
            a. Member has mild ARIA-E on MRI and is asymptomatic or has mild clinical symptoms
        ii. Dosing should be suspended until MRI demonstrates radiographic resolution and symptoms resolve for members that meet any of the following criteria:
            a. Member has mild ARIA-E on MRI and has moderate or severe clinical symptoms
            b. Member has moderate ARIA-E on MRI and is asymptomatic or has mild, moderate, or severe clinical symptoms
            c. Member has severe ARIA-E on MRI and is asymptomatic or has mild, moderate, or severe clinical symptoms
    2. For members with radiographic evidence of ARIA-H:
        i. Dosing may continue for members that meet the following criteria:
            a. Member has mild ARIA-H on MRI and is asymptomatic
        ii. Dosing should be suspended until MRI demonstrates radiographic stabilization and symptoms resolve for members that meet any of the following criteria:
            a. Member has mild ARIA-H on MRI and is symptomatic
            b. Member has moderate ARIA-H on MRI and is asymptomatic or symptomatic
            c. Member has severe ARIA-H on MRI and is asymptomatic or symptomatic

Authorization of 12 months (reauthorizations beyond initial 18 months of therapy) may be granted for members requesting continuation of therapy when all of the following criteria are met:

A. Member has met all initial authorization criteria at the time of initial approval.
B. Member has a positive clinical response as evidenced by stabilization or slowing of disease progression as documented by any of the following (Note: repeat assessment tool(s) must be the same tool that was submitted upon initial request):
    1. CDR-Global Score (i.e., score of 0.5 or 1)
    2. MMSE (i.e., decline of 3 points or less per year)
    3. MoCA (i.e., score of greater than or equal to 16)
    4. St. Louis University Mental State Exam (SLUMS) score of greater than or equal to 16

Other

Leqembi (lecanemab-irmb) considered not medically necessary for members who do not meet the criteria set forth above.

Appendices

Appendix A: Summary of clinical and cognitive evaluation for MCI due to AD

- Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e. historical or observed evidence of decline over time)
- Objective evidence of impairment in one or more cognitive domains, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains)
- Preservation of independence in functional abilities
- No dementia

Appendix B: Clinical Dementia Rating (CDR) Scale

The CDR is obtained through semi-structured interviews of patients and informants with cognitive functioning rated on a 5-point scale in the following domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The score relates to the member's level of dementia:

- 0 = Normal
- 0.5 = Very Mild Dementia
- 1 = Mild Dementia
- 2 = Moderate Dementia
- 3 = Severe Dementia

Appendix C: Mini-Mental Status Exam (MMSE)

The MMSE is scored on a 30-point scale, with items that assess orientation (temporal and spatial; 10 points), memory (registration and recall; 6 points), attention/concentration (5 points), language (verbal and written, 8 points), and visuospatial function (1 point). The score relates to the member's level of dementia:

- 25 – 30 suggests normal cognition
- 20 – 24 suggests mild dementia
- 13 – 20 suggests moderate dementia
- Less than 12 suggests severe dementia

Appendix D: Montreal Cognitive Assessment (MoCA)

Per MoCA assessment, average scores for the following ranges are:

- Mild Cognitive Impairment: 19 – 25
- Mild Dementia: 11 – 21
- Normal: 26 and above

Appendix E: ARIA MRI Classification Criteria

ARIA Type	Radiographic Severity		
	Mild	**Moderate**	**Severe**
ARIA-E	FLAIR hyperintensity confined to sulcus and or cortex/subcortical white matter in one location < 5 cm	FLAIR hyperintensity 5 to 10 cm, or more than 1 site of involvement, each measuring < 10 cm	FLAIR hyperintensity measuring > 10 cm with associated gyral swelling and sulcal effacement. One or more separate/independent sites of involvement may be noted.

ARIA-H microhemorrhage	≤ 4 new incident microhemorrhages	5 to 9 new incident microhemorrhages	10 or more new incident microhemorrhages
ARIA-H superficial siderosis	1 focal area of superficial siderosis	2 focal areas of superficial siderosis	> 2 areas of superficial siderosis

CLINICAL RATIONALE

On January 6, 2023, the U.S. Food and Drug Administration (FDA) approved the monoclonal antibody, Leqembi (Lecanemab-irmb), for the treatment of Alzheimer's Disease (AD), a neurodegenerative disorder resulting in progressive cognitive and behavioral decline, based on the surrogate endpoint of reduction of amyloid beta plaque in the brain. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied.

Efficacy

The efficacy of Leqembi was evaluated in a phase IIb (Study 201, N = 854) multinational, double-blind, placebo-controlled trial in which the primary outcome was the change from baseline in Alzheimer's Disease Composite Score (ADCOMS) score at month 12 compared with placebo; superiority was determined if a pre-specified 80% probability threshold for being better than placebo with 25% less decline was achieved. Inclusion was limited to those with early AD (i.e., mild cognitive impairment [MCI] or mild dementia due to AD). Results of the trial found that the Leqembi (lecanemab-irmb) 10 mg/kg every 2 weeks dose resulted in a 64% probability of being better than placebo, thus failing to achieve significant improvement for the primary outcome. Despite this, the FDA voted to approve Leqembi (lecanemab-irmb) based on the secondary outcome results indicating a significant decline in Aβ plaque, a surrogate endpoint that has been determined to be reasonably likely to predict clinical benefit.

Leqembi was also evaluated in a phase III (CLARITY AD, N = 1,734) multinational, double-blind, placebo-controlled, randomized clinical trial with a primary outcome of change in Clinical Dementia Rating-Sum-of-Boxes (CDR-SB) from baseline to 18 months. Leqembi reached statistical significance for the primary outcome as well as the secondary outcomes of change from baseline to 18 months in amyloid burden on PET, ADAS-cog14 score, AD Composite score, and in the ADCS-MCI-ADL score.

Safety

Leqembi can cause amyloid related imaging abnormalities-edema (ARIA-E), which can be observed on magnetic resonance imaging (MRI) as brain edema or sulcal effusions, and amyloid related imaging abnormalities-hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis. Patients were excluded from enrollment in Study 201 for the following risk factors for intracerebral hemorrhage: 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 severe small vessel or white matter disease. Caution should be exercised when considering the use of LEQEMBI in patients with these risk factors.

A regulatory-imposed protocol amendment was enacted after 300 patients had been enrolled in Study 201 which prohibited further enrollment of ApoE ε4 carriers, as well as required discontinuation of ApoE ε4 carriers that had received Leqembi (lecanemab-irmb) for less than 6 months. This update was requested due to increased rates of ARIA with edema (ARIA-E) in those randomized to Leqembi. ApoE ε4 carriers were subsequently allowed to enroll in CLARITY AD and comprised approximately 15% of the study population. A similar elevated risk of ARIA-E among ApoE ε4 carriers compared to noncarriers was observed; patients should be informed of this risk and that is testing available to determine ApoE ε4 status.

Long-Term Data (36 months):

The most recent open-label extension data through 36 months provides critical new evidence supporting sustained benefit. Key findings include:

- Early-start participants maintained their clinical advantage over delayed-start participants throughout months 18-36, demonstrating that treatment effects persist and that earlier initiation provides benefits that cannot be fully recaptured by delayed treatment
- A subgroup with low baseline pathology (low amyloid or tau burden) showed stability or improvement between 18-36 months, providing support for early treatment initiation
- Sustained amyloid suppression throughout the 36-month period with corresponding improvements in plasma biomarkers
- No new safety signals emerged with long-term treatment
    - ARIA rates decreased substantially after the first 6 months of treatment

The clinical significance of the observed effects remains debated. Independent estimates suggest the minimal clinically important difference (MCID) for CDR-SB is approximately 1.0 point—double the 0.45-point difference observed in Clarity AD. However, the 0.5-point difference may represent meaningful functional distinctions such as driving independently versus requiring supervision for outings, with the potential for greater cumulative benefit with longer treatment duration.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- J0174 – injection, lecanemab-irmb, 1 mg (effective 7/6/2023)

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- Elecsys Phospho-Tau (181P) CSF 2022-12.

POLICY HISTORY

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