Original Effective Date: 05/31/2023
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Last P&T Approval/Version: 10/25/2023
Next Review Due By: 10/2024
Policy Number: C25201-A

LEQEMBI (lecanemab-irmb)

PRODUCTS AFFECTED

Leqembi (lecanemab-irmb)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.
This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Alzheimer's disease

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review.

A. ALZHEIMER'S DISEASE:
   1. Documentation of a diagnosis of mild cognitive impairment (MCI) due to Alzheimer's disease based on NIA-AA diagnostic criteria [A concern regarding cognition reported by the patient or informant or observed by the clinician, Objective evidence of impairment in one or more cognitive domains that is not explained by age or education, Preservation of independence in functional abilities, Not

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demented] OR diagnosis of Alzheimer disease dementia based on NIA-AA criteria for probable AD dementia [See Appendix]
AND

2. Documentation of Clinical Dementia Rating Scale (CDR) Global Score of 0.5 OR Mini-Mental State Examination (MMSE) score between 24 and 30 OR Montreal Cognitive Assessment (MoCA) score between 24 and 30
AND
3. Documentation of confirmation of underlying amyloid beta pathology [through PET scan OR lumbar puncture (LP) for CSF (cerebrospinal fluid)]
AND
4. Documentation within medical record member does NOT have any medical or neurological condition (other than Alzheimer's Disease) that might be a contributing cause of the member's cognitive impairment

CONTINUATION OF THERAPY:

A. ALZHEIMER'S DISEASE:

1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
AND
2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity such as amyloid-related imaging abnormalities (ARIA)
AND
3. Documentation of positive clinical response, as demonstrated by improvement OR stabilization in baseline cognitive scoring using the same testing method as provided during initial authorization request.
AND
4. Documentation of new MRI prior to the 5^{TH}, 7^{TH} and 14^{TH} infusions, if applicable, showing radiographic stability.
Note: If 10 or more new incident microhemorrhages or > 2 focal areas of superficial siderosis (radiographic severe ARIA-H) is 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)

DURATION OF APPROVAL:

Initial authorization: 3 months, Continuation of Therapy: 6 months

PRESCRIBER REQUIREMENTS:

Prescribed by or in consultation with a Neurologist, Geriatrician, Geropsychiatric specialist OR Alzheimer's Disease Specialist [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

50 years of age and older

QUANTITY:

10 mg/kg once every two weeks.

PLACE OF ADMINISTRATION:

The recommendation is that infused medications in this policy will be for pharmacy or medical benefit coverage administered in a place of service that is a non-inpatient hospital facility-based location.

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DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Intravenous

DRUG CLASS:
Alzheimer's Treatment - Anti-Amyloid Antibodies

FDA-APPROVED USES:
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.

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:

Criteria for all-cause dementia: Core clinical criteria

The diagnosis of dementia is intended to encompass the spectrum of severity, ranging from the mildest to the most severe stages of dementia. The methodology for staging of dementia severity was beyond the charge of the workgroup. Dementia is diagnosed when there are cognitive or behavioral (neuropsychiatric) symptoms that:

1. Interfere with the ability to function at work or at usual activities; and
2. Represent a decline from previous levels of functioning and performing; and
3. Are not explained by delirium or major psychiatric disorder.
4. Cognitive impairment is detected and diagnosed through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment, either a "bedside" mental status examination or neuropsychological testing. Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis.
5. The cognitive or behavioral impairment involves a minimum of two of the following domains:

a. Impaired ability to acquire and remember new information—symptoms include repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route.

b. Impaired reasoning and handling of complex tasks, poor judgment— symptoms include poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities.

c. Impaired visuospatial abilities—symptoms include inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements, or orient clothing to the body.

d. Impaired language functions (speaking, reading, writing)—symptoms include difficulty thinking of common words while speaking, hesitations; speech, spelling, and writing errors.

e. Changes in personality, behavior, or comportment—symptoms include uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, socially unacceptable behaviors

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Probable AD dementia is diagnosed when the patient:

1. Meets criteria for dementia described above, and in addition, has the following characteristics:
   A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days.
   B. Clear-cut history of worsening of cognition by report or observation; and
   C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories.
      a. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text.
      b. Non-amnestic presentations:

      • Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present.

      • Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present.

      • Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.
   D. The diagnosis of probable AD dementia ***should not*** be applied when there is evidence of (a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) core features of Dementia with Lewy bodies other than dementia itself; or (c) prominent features of behavioral variant frontotemporal dementia; or (d) prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurological disease, or a non- neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

Common Cognitive Assessments

Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog 13) A 13-item test used to measure the amount or degree of cognitive impairment based on the domains of attention, concentration, memory, language, and praxis. It is currently the preferred test for measuring the effectiveness of anti-dementia treatments, with current studies taking place in the MCI population. Because the ADAS-Cog is given verbally with a heavy emphasis on spoken language, the patient must be fluent in the language in which the test is given. The ADAS-Cog is translated into 81 languages.

Clinical Dementia Rating Scale–Sum of Boxes (CDR–SB) Uses a 5-point scale that identifies 6 cognitive and functional performance domains affected by AD and other dementias. Information is acquired through patient interviews and reliable reporting from a caregiver or member of the patient's family. This test has been shown to be effective in correctly staging AD and MCI. This test is available in more than 40 languages.

Mini-Cognitive Assessment Instrument (Mini-Cog) A 3-minute assessment used as part of a complete diagnostic workup designed to help detect cognitive impairment in older adults. In the Mini-Cog, the patient is asked to recall 3 items and then draw a clock. The test is accurate and accessible to many populations, including non-English speakers.

Mini-Mental State Examination (MMSE) A test that measures cognition and has been used to stage

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and show changes over time. This assessment is available in more than 70 languages and dialects

Self- Administered Gerocognitive Examination (SAGE) measures cognitive function in the domains of orientation, language, memory, executive function, calculations, abstraction and visuospatial abilities. Takes roughly 10-15 minutes to complete.

St Louis University Mental Status (SLUMS) Measures cognitive function in the domains of orientation, attention (digit span), numeric calculation, immediate and delayed verbal recall, verbal fluency (animal naming), executive functions, figure recognition/size differentiation and immediate recall of contextual verbal information- takes 7 minutes to complete.

Montreal Cognitive Assessment (MoCA) Brief screening measure consisting of a 30-point test administered in 10 minutes, focusing on memory, visuospatial, executive and language function and orientation to time and place.

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Leqembi is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta. It reduces amyloid beta plaques in the brain, which is a defining pathophysiological feature of Alzheimer disease.

The efficacy of Leqembi was evaluated in a double-blind, placebo-controlled, parallel-group dose-finding trial, Study 201 (NCT01767311) in adult patients with AD (patients with confirmed presence of amyloid pathology and MCI or mild dementia consistent with Stage 3 and Stage 4 AD). The study assessed three doses across two regimens of Leqembi. Study 201 had a 79-week double-blind, placebo-controlled period, followed by an open-label extension (OLE) period for up to 260 weeks, which was initiated after a gap period (range, 9 to 59 months; mean, 24 months) off treatment. Change from baseline in brain amyloid plaque, as measured by 18F-florbetapir PET and quantified by a composite standard uptake value ratio (SUVR), was assessed in a subset of patients at Weeks 53 and 79. These data, served as the endpoint supporting accelerated approval. Compared with placebo, the Leqembi 10 mg/kg biweekly arm demonstrated a statistically significant reduction in brain amyloid plaque at Week 79 (mean difference of −0.31 SUVR or −73.5 Centiloids; P <0.001).

In Study 201, the most common adverse reactions reported in at least 5% of patients treated with Leqembi 10 mg/kg biweekly (n = 161) and having at least 2% higher incidence than in patients on placebo (n = 245) were infusion-related reactions (Leqembi 20%; placebo 3%), headache (Leqembi 14%; placebo 10%), ARIA-E (Leqembi 10%; placebo 1%), cough (Leqembi, 9%; placebo, 5%) and diarrhea (Leqembi, 8%; placebo, 5%). The most common adverse reactions leading to discontinuation of Leqembi were infusion-related reactions (e.g., flu-like symptoms, nausea, vomiting and changes in blood pressure), which led to discontinuation in 2% (4/161) of patients treated with Leqembi compared to 1% (2/245) of patients on placebo.

Risk Factors for Intracerebral Hemorrhage

Patients were excluded from enrollment in Study 201 for baseline use of anticoagulant medications. Antiplatelet medications such as aspirin and clopidogrel were allowed. Patients who received Leqembi and an antithrombotic medication (i.e., aspirin, other antiplatelets, or anticoagulants) did not have an increased risk of ARIA with hemosiderin deposition (ARIA-H; includes microhemorrhage and superficial siderosis) 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 Leqembi, additional caution should be exercised when considering the administration of antithrombotics or a thrombolytic

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agent (e.g., tissue plasminogen activator [tPA]) to a patient already being treated with Leqembi. Additionally, 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.

Leqembi received traditional FDA approval in July 2023 based on the results of the phase 3 Clarity AD trial. The primary efficacy endpoint was reduction in clinical decline compared to placebo, as measured by the CDR-SB. On this endpoint, Leqembi showed a statistically significant 27% reduction in clinical decline compared to placebo at 18 months (a 0.45-point difference on the CDR-SB score). Most experts consider this clinical benefit to be modest, yet significant, due to the current lack of more effective treatment alternatives. During the trial, 12.6% and 17.3% of patients with early-stage AD who received Leqembi developed ARIA-E and ARIA-H, respectively.

The label update also includes the addition of a black box warning for amyloid related imaging abnormalities. Warning is inclusive of ApoE ε4 homozygotes who were found to have a higher incidence of ARIA compared to heterozygotes and noncarriers.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of LEQEMBI (lecanemab-irmb) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to LEQEMBI (lecanemab-irmb) include: patients with serious hypersensitivity to lecanemab-irmb or to any of the excipients of Leqembi.

OTHER SPECIAL CONSIDERATIONS:
Leqembi (lecanemab) has a Black Box Warning for amyloid related imaging abnormalities. Monoclonal antibodies directed against aggregated forms of beta amyloid, including 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. Patients treated with this class of medications, including 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 Leqembi for the treatment of Alzheimer's disease and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment with Leqembi.

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
J0174	Injection, lecanemab-irmb, 1 mg

AVAILABLE DOSAGE FORMS:
Leqembi SOLN 200MG/2ML (100 mg/mL) in a single-dose vial
Leqembi SOLN 500MG/5ML (100 mg/mL) in a single-dose vial

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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information FDA-Approved Uses Background and Other Considerations Contraindications/Exclusions/Discontinuation Other Special Considerations Coding/Billing Information References	Q4 2023
NEW CRITERIA	Q2 2023

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