UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Neurology – Leqembi Utilization Management Medical Policy
- Leqembi™ (lecanemab-irmb intravenous infusion – Eisai/Biogen)

REVIEW DATE: 4/26/2024, 8/8/2024

OVERVIEW

Leqembi, an amyloid beta-directed antibody, is indicated for the **treatment of Alzheimer's disease**.[1] 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.

Disease Overview

An estimated 6.5 million Americans ≥ 65 years of age are living with Alzheimer's dementia in 2022, with 73% of these people ≥ 75 years of age.[2] The number and proportion of older adults who have mild cognitive impairment due to Alzheimer's disease is difficult to estimate; however, a rough approximation suggests that 5 million older Americans may have mild cognitive impairment due to Alzheimer's disease. People with mild cognitive impairment due to Alzheimer's disease have biomarker evidence of brain changes due to the disease in addition to subtle problems with memory and thinking. Biomarker evidence includes abnormal levels of amyloid beta as evidenced on positron emission tomography (PET) scans and in analysis of cerebrospinal fluid, and decreased metabolism of glucose as shown on PET scans. These cognitive problems may be noticeable to the individual family members and friends, but not to others, and they do not interfere with the person's ability to carry out everyday activities. The mild changes in cognitive abilities occur when the brain can no longer compensate for the damage and death of nerve cells due to Alzheimer's disease. Among those with mild cognitive impairment, about 10% to 15% develop dementia each year. Approximately one-third of people with mild cognitive impairment develop Alzheimer's dementia within 5 years.

POLICY STATEMENT

Lecanemab-irmb may be covered for patients with mild cognitive impairment due to Alzheimer's disease and mild Alzheimer's disease dementia when diagnosis is confirmed with appropriate testing as indicated in the criteria.

Leqembi (lecanemab-irmb) may be covered for the treatment of Alzheimer's disease (AD) in patients who meet all of the following criteria:

For **initial therapy**, **all** of the following:
Diagnosis of **one** of the following based on National Institute on Aging and the Alzheimer's Association (NIA-AA) criteria:
- Mild cognitive impairment (MCI) due to Alzheimer's disease; **or**
- Probable Alzheimer's disease dementia

and
Submission of medical records (e.g., chart notes, laboratory values) documenting **all** of the following
- Global Clinical Dementia Rating (CDR) score of 0.5 or 1.0; **and**
- **One** of the following:
  - Mini-Mental State Examination (MMSE) score of 22 - 28
  - Saint Louis University Mental Status (SLUMS) score of 17 or greater
  - Montreal Cognitive Assessment (MoCA) score of 11- 25

and
Submission of medical records (e.g., chart notes, laboratory values) documenting the presence of beta-amyloid protein deposition, as evidenced by **one** of the following:

- Positive amyloid positron emission tomography (PET) scan; **or**
- Cerebrospinal fluid (CSF) biomarker testing documents abnormalities suggestive of beta-amyloid accumulation in the brain (e.g., Aβ42: 40 ratio, p-tau/Aβ42)

and
Other differential diagnoses [e.g., dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), vascular dementia, pseudodementia due to mood disorder, vitamin B12 deficiency, encephalopathy, etc.] have been ruled out;
and
One of the following:

- Patient is not currently taking an anticoagulant (e.g., warfarin, dabigatran); **or**
- **Both** of the following:
  - Patient is currently taking an anticoagulant (e.g., warfarin, dabigatran); **and**
  - Counseling has been provided that the combined use of Leqembi with anti-coagulant drugs may increase the risk of cerebral macrohemorrhage and prescriber attests that the patient has shared in decision-making to initiate Leqembi therapy

and

Patient has no history of intracerebral hemorrhage [e.g., transient ischemic attack (TIA), stroke] within the previous year prior to initiating treatment; **and**
Counseling has been provided on the risk of amyloid-related imaging abnormalities (ARIA-E and ARIA-H) and patient is aware to monitor for headache, dizziness, visual disturbances, nausea, and vomiting; **and**
All of the following:

- Precivity testing for ApoE ε4 status
- Counseling has been provided on how testing for ApoE ε 4 status informs the risk of developing ARIA when deciding to initiate treatment with Leqembi; **and**
- The patient and prescriber attests that the patient has shared in decision-making to initiate Leqembi therapy

and

- A baseline brain magnetic resonance imaging (MRI) has been completed within 12 months prior to initiating treatment; **and**
- Not used in combination with other Aβ monoclonal antibodies (mAbs) for Alzheimer's Disease (e.g., Aduhelm); **and**
- Prescribed by a neurologist, geriatric psychiatrist, or geriatrician who specializes in treating dementia; **and**
- Prescriber and/or member must currently be enrolled in a patient registry that collects information on treatments for Alzheimer's disease- Alzheimer Network for Treatment and Diagnostics (ALZ-NET); **and**
- Leqembi dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
- Initial authorization will be for no more than 6 months

• For **continuation of therapy**, **all** of the following:
Patient continues to have one of following diagnoses based on National Institute on Aging and the Alzheimer's Association (NIA-AA) criteria

- Mild cognitive impairment (MCI) due to Alzheimer's disease; **or**
- Probable Alzheimer's disease dementia

and

Submission of current medical records (e.g., chart notes, laboratory values) documenting that the patient continues to meet **all** of the following (updated assessments must be measured no earlier than 4 weeks prior to a continuation request):

- Global Clinical Dementia Rating (CDR) score of 0.5 or 1.0; **and**
- **One** of the following:
- Mini-Mental State Examination (MMSE) score of 22 - 28

- Saint Louis University Mental Status (SLUMS) score of 17 or greater
- Montreal Cognitive Assessment (MoCA) score of 11- 25

and

Both of the following:
Submission of medical records (e.g., chart notes) confirming follow-up brain magnetic resonance imaging (MRI) has been completed after the initiation of therapy and prior to the 5th and 7th infusion treatment; **and**
One of the following:
- ARIA has not been observed on MRI; **or**
- All of the following:
  - ARIA has been observed on MRI; **and**
    - Prescriber attests that continuation of therapy with Leqembi is appropriate based on the severity of the patient's clinical symptoms; **and**
    - **One** of the following:
      - Follow-up MRI demonstrates radiographic resolution and/or stabilization; **or**
      - Prescriber attests that continuation of therapy with Leqembi is appropriate based on the radiographic severity of ARIA

and
- Not used in combination with other Aβ monoclonal antibodies (mAbs) for Alzheimer's Disease (e.g., Aduhelm); **and**
- Prescribed by a neurologist, geriatric psychiatrist, or geriatrician who specializes in treating dementia; **and**
- Leqembi dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
- Reauthorization is for no more than 12 months

Background

Alzheimer's disease (AD) is the most common cause of dementia and accounts for an estimated 60% to 80% of cases[1]. After AD, the most common neurodegenerative dementias are Lewy body disease, characterized by chronic rapid eye movement (REM) sleep behavior disorder, early visuospatial impairment, and parkinsonism; and Frontotemporal dementia, characterized by a behavioral variant or less often, a language impairment variant.

AD is characterized by deposition of amyloid-beta Aβ plaques and neurofibrillary tangles (comprised of abnormal tau protein) in the brain, accompanied by synaptic dysfunction and neurodegeneration.[3,4] The deposition of Aβ (as amyloid plaques) generally begins decades before any symptoms of AD are observed. More specifically, Aβ deposition is followed sequentially by markers of neurodegeneration, accumulation of tau pathology, and brain volume loss. This pre-symptomatic phase of AD will precede the emergence of AD symptoms 10 to 20 years prior.[5]

Tau is the microtubule associated protein (MAP) of a normal mature neuron. Tau is a phosphoprotein that promotes the assembly of tubulin into microtubules and stabilization of their structure. In AD (and certain other related neurodegenerative diseases, called tauopathies), tau protein is abnormally hyperphosphorylated and aggregated into bundles of filaments. In AD, this tau pathology is seen as intraneuronal neurofibrillary tangles of paired helical filaments sometimes admixed with straight filaments. Aggregates of abnormally hyperphosphorylated filaments are also seen in dystrophic neurites surrounding the Aβ plaque core, and in the neuropil as neuropil threads.[6]

There are 2 ways to detect abnormal Aβ, either directly via PET imaging using tracers or indirectly by measuring the levels of the long form of Aβ in the CSF. P-tau and t-tau can also be detected using CSF and are used as biomarkers to detect the emergence of AD in patients with MCI.

Age of AD onset:
Typical AD: AD is characteristically a disease of older age. The incidence and prevalence of AD increase exponentially with age, essentially doubling in prevalence every 5 years after the age of 65 years.
Early-onset dementia: Although less common, early-onset dementia occurs in patients < 65 years of age. These patients often present with symptoms somewhat atypical for this disease, such as language, visual, or mood-behavioral changes rather than predominant memory loss. A study from the United Kingdom estimated that the

incidence of dementia in individuals 30 to 65 years of age was approximately 54 per 100,000 person-years. The most common cause of dementia in these patients was AD (34%), followed by vascular dementia (18%), frontotemporal dementia (12%), dementia with Lewy bodies (7%), and alcohol-related dementia (10%).[9]
Inherited forms of AD: These forms of AD are rare (< 1% of all AD cases) and routinely present before 65 years of age, frequently in the fifth decade or earlier. Inherited forms of AD typically exhibit an autosomal-dominant inheritance pattern related to mutations in genes that alter Aβ protein production or metabolism, including amyloid precursor protein (APP), presenilin-1 (PSEN1), and presenilin-2 (PSEN2).
AD associated with Down syndrome: Patients with Down syndrome have an additional gene dose of APP due to trisomy of chromosome 21 and inevitably develop AD pathology. Symptoms tend to emerge at an earlier age, i.e., 10 to 20 years earlier than the general population with AD.

Risk factors for AD:[2]

- Aging is an important risk factor for dementia. AD affects 5% to 10% of people > 65 years of age, and 50% of those ≥ 85 years of age.
- Nonmodifiable risk factors for AD include female gender, Black race, Hispanic ethnicity, and genetic factors such as presence of the APOE gene.
- Modifiable risk factors for all-cause dementia include hypertension, diabetes, diet, and limited cognitive, physical, and social activities.

While the genetic basis for early-onset AD is much better understood, the genetic basis of late-onset AD is considered far more complex, with susceptibility conferred by a variety of more common but less penetrant genetic factors likely interacting with environmental and epigenetic influences. To date, the most firmly established genetic risk factor for late-onset disease is APOE:

- The APOE gene is located on chromosome 19 and exists in 3 alleles: epsilon 2, 3, and 4. The APOE epsilon 4 (ε4) allele has been confirmed to be an important risk factor for AD in many clinical trials.
- Factors that may influence the impact of APOE ε4 on AD risk include female gender, African/African-American race (although there are conflicting data), vascular risk factors (e.g., smoking, diabetes, hypertension, and hypercholesterolemia), and modifier genes/environment.
- Genetic testing is available for the known causative genes in early-onset AD but has not been widely adopted, likely in part because of the current lack of highly effective preventive or therapeutic strategies.

The symptoms at early stage AD are less pronounced than in later stages of AD, and therefore require measures that are different from those used in later stages.

The Clinical Dementia Rating-Sum of Boxes (CDR-SB) is an integrated scale that assesses both daily function and cognitive effects and was shown to be sufficiently sensitive and specific to detect change over time in early symptomatic AD patients. The scale integrates assessments from 3 domains of cognition (memory, orientation, judgment/problem-solving) and 3 domains of function (community affairs, home/hobbies, personal care). CDR-SB scores range from 0-18, with higher scores indicating greater disease severity. A minimal clinically important difference in CDR-SB has not been clearly defined but has been estimated to be 1-2 points.[5,11,41] A CDR-SB score ranging from 0.5 - 4.0 has been reported to correspond to a CDR-G score of 0.5. A CDR-SB score ranging from 4.5-9.0 has been reported to correspond to a CDR-G score of 1.

CDR-SB Score	Disease Severity
0	Normal
0.5 - 4.0	Suggests questionable cognitive impairment to very mild dementia
0.5 - 2.5	Suggests questionable cognitive impairment
3.0 - 4.0	Suggests very mild dementia
4.5 - 9.0	Suggests mild dementia
9.5 - 15.5	Suggests moderate dementia
16.0 - 18.0	Suggests severe dementia

The Mini-Mental State Exam (MMSE) is a widely used performance-based test of global cognitive status. The MMSE is a measure of cognition that includes 11 tasks relating to topics of word recall, attention and calculation, language

ability, and visuospatial function. The scale ranges from 0 to 30 with a lower score reflecting greater cognitive impairment. It has several known limitations impacting sensitivity to change, particularly in earlier disease stages: substantial ceiling effects, sensitivity to practice effects, scores are impacted by patients' educational achievement, and learning effects are observed. The minimal clinically important difference of the MMSE in AD is estimated to be 1-3 points, and in early AD to be 1-2 points.[5]

MMSE Score	Disease Severity
25 - 30	Normal to questionable cognitive impairment
19 - 24	Suggests mild dementia
10 - 18	Suggests moderate dementia
0 - 9	Suggests severe dementia

The Alzheimer's Disease Assessment Scale – Cognitive Subscale (13-Item version) (ADAS-Cog13) comprises both cognitive tasks and clinical ratings of cognitive performance. The scale items capture word recall, ability to follow commands, the ability to correctly copy or draw an image, naming, the ability to interact with everyday objects, orientation, word recognition, memory, comprehension of spoken language, word-finding, and language ability, with a measure for delayed word recall and concentration/distractibility. The total score ranges from 0 to 85 with an increase in score over time indicates increasing cognitive impairment. The minimal clinically important difference of the ADAS-COG 13 in early AD is estimated to be 3 points.[5]

The Montreal Cognitive Assessment (MoCA) is a widely used screening test specifically designed to detect more subtle cognitive deficits that characterize mild cognitive impairment. Like the MMSE, the MoCA is scored on a 30-point scale, with items that assess delayed word recall, visuospatial/executive function, language, attention/concentration, and orientation. Studies examining head-to-head performance of patients on the MMSE and MoCA have shown that the MoCA is more difficult; MoCA scores are consistently lower than those obtained on the MMSE. The MoCA appears to be more sensitive than the MMSE for detecting MCI, though perhaps slightly less specific. A minimum clinically important difference of the MoCA in AD has not been described.

Assessment Scale	Minimal Clinical Important Difference
Clinical Dementia Rating-Sum of Boxes (CDR-SB)	1-2 points
Mini-Mental State Exam (MMSE)	1-3 points
Alzheimer's Disease Assessment Scale – Cognitive Subscale (13-Item version) (ADAS-Cog13)	3 points

The stages of AD dementia can be defined by the MMSE and MoCA scores below:[12]

- Mild dementia (MMSE 19 to 26; MoCA 12 to 16)
- Moderate dementia (MMSE 10 to 18; MoCA 4 to 11)
- Severe dementia (MMSE < 10; MoCA < 4)

The National Institute on Aging and the Alzheimer's Association (NIA-AA) research framework committee created a numeric clinical staging scheme (table below) applicable for diagnosing those in the Alzheimer's continuum. This staging scheme reflects the sequential evolution of AD from an initial stage characterized by the appearance of abnormal AD biomarkers in asymptomatic individuals. As biomarker abnormalities progress, the earliest subtle symptoms become detectable.

Stage	Numeric Clinical Staging—Applicable Only to Individuals in the Alzheimer's Continuum
Stage 1	• Performance within expected range on objective cognitive tests. Cognitive test performance may be compared to normative data of the investigator's choice, with or without adjustment (the choice of the investigators) for age, sex, education, etc.* • Does not report recent decline in cognition or new onset of neurobehavioral symptoms of concern. • No evidence of recent cognitive decline or new neurobehavioral symptoms by report of an observer (e.g., study partner) or by longitudinal cognitive testing if available.
Stage 2	• Normal performance within expected range on objective cognitive tests. • Transitional cognitive decline: Decline in previous level of cognitive function, which may involve any cognitive domain(s) (i.e., not exclusively memory). • May be documented through subjective report of cognitive decline that is of concern to the participant. • Represents a change from individual baseline within past 1–3 years, and persistent for at least 6 months. • May be corroborated by informant but not required. • Or may be documented by evidence of subtle decline on longitudinal cognitive testing but not required. • Or may be documented by both subjective report of decline and objective evidence on longitudinal testing. • Although cognition is the core feature, mild neurobehavioral changes—for example, changes in mood, anxiety, or motivation—may coexist. In some individuals, the primary compliant may be neurobehavioral rather than cognitive. Neurobehavioral symptoms should have a clearly defined recent onset, which persists and cannot be explained by life events† • No functional impact on daily life activities.
Stage 3	• Performance in the impaired/abnormal range on objective cognitive tests. • Evidence of decline from baseline, documented by the individual's report or by observer (e.g., study partner) report or by change on longitudinal cognitive testing or neurobehavioral behavioral assessments. • May be characterized by cognitive presentations that are not primarily amnestic‡ • Performs daily life activities independently, but cognitive difficulty may result in detectable but mild functional impact on the more complex activities of daily life, that is, may take more time or be less efficient but still can complete, either self-reported or corroborated by a study partner.
Stage 4	• Mild dementia. • Substantial progressive cognitive impairment affecting several domains, and/or neurobehavioral disturbance. Documented by the individual's report or by observer (e.g., study partner) report or by change on longitudinal cognitive testing. • Clearly evident functional impact on daily life, affecting mainly instrumental activities. No longer fully independent/requires occasional assistance with daily life activities.
Stage 5	• Moderate dementia. • Progressive cognitive impairment or neurobehavioral changes. Extensive functional impact on daily life with impairment in basic activities. No longer independent and requires frequent assistance with daily life activities.
Stage 6	• Severe dementia. • Progressive cognitive impairment or neurobehavioral changes. Clinical interview may not be possible. • Complete dependency due to severe functional impact on daily life with impairment in basic activities, including basic self-care.

Stage	Numeric Clinical Staging—Applicable Only to Individuals in the Alzheimer's Continuum
Notes	*For stages 1-6: Cognitive test performance may be compared to normative data of the investigator's choice, with or without adjustment (choice of the investigators) for age, sex, education, etc. † For stages 2-6: Although cognition is the core feature, neurobehavioral changes – for example, changes in mood, anxiety, or motivation – may coexist. ‡ For stages 3-6: Cognitive impairment may be characterized by presentations that are not primarily amnestic.

REFERENCES

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4. Sevigny, J., Chiao, P., Bussière, T. et al. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature 537, 50-56 (2016).
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HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/25/2023
Update	7/19/2023: Leqembi received traditional approval by the FDA on July 6, 2023 based on results from the CLARITY AD trial. No criteria changes.	--