Oscar Clinical Guideline: Leqembi (lecanemab-irmb) (PG138, Ver. 5)

Leqembi (lecanemab-irmb)

- Lequembi (lecanemab-irmb), for intravenous use
- Leqembi Iqlik (lecanemab-irmb), for subcutaneous use

Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Summary

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the gradual decline of cognitive functions, including memory, thinking, and reasoning abilities. It is the most common cause of dementia in older adults, affecting millions of people worldwide. While the majority of cases occur in individuals over 65 years of age, early-onset Alzheimer's can develop in people as young as 40.

The exact cause of Alzheimer's disease is not fully understood, but it is believed to result from a combination of genetic, environmental, and lifestyle factors. At the microscopic level, the disease is associated with the accumulation of amyloid-beta (Aβ) plaques and neurofibrillary tangles in the brain, which contribute to neuronal dysfunction and cell death.

Currently, there is no cure for Alzheimer's disease. Treatment focuses on managing symptoms, slowing disease progression, and improving the quality of life for patients and their caregivers. Available treatments can be categorized into symptomatic treatments, disease-modifying therapies, and non-pharmacological interventions:

- Symptomatic treatments: These medications aim to alleviate cognitive and behavioral symptoms, such as memory loss and confusion. Commonly used drugs include cholinesterase inhibitors (e.g., donepezil, rivastigmine, and galantamine) and the NMDA receptor antagonist memantine. While these treatments can help manage symptoms, they do not address the underlying disease progression.
- Disease-modifying therapies: Disease-modifying therapies target the underlying pathophysiology of Alzheimer's disease, with the goal of slowing or halting its progression. Two notable examples of these therapies include Leqembi (lecanemab-irmb) and Kisunla (donanemab-azbt), both of which are amyloid beta-directed antibodies designed to reduce amyloid plaque accumulation in the brain.
- Non-pharmacological interventions: A comprehensive approach to Alzheimer's disease management includes non-pharmacological strategies, such as cognitive stimulation, physical activity, and social engagement. These interventions play a critical role in preserving cognitive function, delaying symptom progression, and improving overall quality of life. Caregiver support and education are also essential components of patient care.

Leqembi (lecanemab-irmb) is a monoclonal antibody that specifically targets aggregated forms of amyloid-beta, promoting their clearance from the brain. It is indicated for the treatment of Alzheimer's disease in patients with mild cognitive impairment or mild dementia stages, consistent with the populations studied in clinical trials. There are no safety or efficacy data to support initiating treatment at earlier or later stages of the disease than those studied.

Leqembi (lecanemab-irmb) has a boxed warning for the risk of amyloid related imaging abnormalities (ARIA), including ARIA-edema (ARIA-E) and ARIA-hemorrhage (ARIA-H). ARIA is typically asymptomatic but can be serious and life-threatening. Hemorrhages greater than 1 centimeter (cm) have occured, and ARIA-E can result in neurological deficits similar in nature to stroke symptoms. Those who are ApoE-ε4 homozygotes are at a higher risk of ARIA, especially symptomatic and serious cases. It is recommended that everyone who initiates Leqembi (lecanemab-irmb) is tested for ApoE-ε4 status and completes regular radiological testing via magnetic resonance imaging (MRI) testing. In August of 2025, the FDA recommended additional MRI testing before the 3rd infusion of Leqembi (lecanemab-irmb) (previously

the recommendation was before the 5th, 7th and 14th infusion), specifically with a goal to identify early cases of ARIA-E

Definitions

"ADAS-Cog (Alzheimer's Disease Assessment Scale - Cognitive Subscale)" is a widely used cognitive test specifically designed to evaluate the cognitive function of individuals with Alzheimer's disease. It assesses various cognitive domains, such as memory, language, praxis, and orientation. The ADAS-Cog has multiple versions with different numbers of items; the 14-item version is often used in clinical trials. Higher scores on the ADAS-Cog indicate greater cognitive impairment.

"ADCOMS (Alzheimer's Disease Composite Score)" is a composite score that combines selected items from the CDR-SB, MMSE, and ADAS-Cog to create a single measure of cognitive and functional performance in Alzheimer's disease. The ADCOMS has been developed specifically for use in clinical trials to detect treatment effects in the early stages of the disease.

"Alzheimer's disease (AD)" is a progressive neurodegenerative disorder characterized by a decline in cognitive functions, such as memory, thinking, and reasoning abilities. It is the most common cause of dementia in older adults.

"Amyloid-beta (A**β**) plaques" are abnormal protein deposits that accumulate in the brain and are associated with Alzheimer's disease. They consist of amyloid-beta peptides, which are thought to contribute to neuronal dysfunction and cell death.

"CDR-SB (Clinical Dementia Rating Scale Sum of Boxes)" is a widely used tool to assess the severity of dementia, particularly Alzheimer's disease. It measures cognitive and functional performance in six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Each domain is rated on a scale from 0 (no impairment) to 3 (severe impairment), resulting in a sum of boxes score ranging from 0 to 18, with higher scores indicating greater severity of dementia.

"Cholinesterase inhibitors" is a class of drugs used to treat Alzheimer's disease by increasing the levels of the neurotransmitter acetylcholine in the brain, which can help improve cognitive function. Examples include donepezil, rivastigmine, and galantamine.

"Dementia" is a general term for a decline in mental ability severe enough to interfere with daily life. It is not a specific disease but an overall term that describes a wide range of symptoms associated with a decline in memory or other thinking skills.

"Disease-modifying therapies" refer to treatments that aim to target the underlying pathophysiology of a disease, with the goal of slowing down or halting its progression.

"Experimental or Investigational" are terms used to describe treatments, procedures, or services that are not considered standard of care or have not been proven to be safe and effective for a specific condition. These treatments are generally not covered by the Plan.

"MMSE (Mini-Mental State Examination)" is a brief, 30-point questionnaire that is used to assess cognitive function in older adults. It measures various cognitive domains, including orientation, registration, attention and calculation, recall, and language. The MMSE is scored from 0 to 30, with lower scores indicating more severe cognitive impairment.

"Neurofibrillary tangles" are abnormal accumulations of the protein tau inside brain cells that are also associated with Alzheimer's disease. These tangles disrupt the normal functioning of cells and are thought to contribute to cell death.

"NMDA receptor antagonist" is a type of drug that blocks the NMDA receptor, a protein involved in the communication between brain cells. Memantine is an NMDA receptor antagonist used to treat Alzheimer's disease.

"PET SUVR (Positron Emission Tomography Standardized Uptake Value Ratio)" is a quantitative measure used in amyloid PET imaging to assess the levels of amyloid-beta plaques in the brain. In the context of Alzheimer's disease, PET SUVR is used to determine the extent of amyloid-beta plaque accumulation in specific brain regions. Higher SUVR values indicate higher levels of amyloid-beta plaques, which are associated with Alzheimer's disease.

"Symptomatic treatments" refers to medications that aim to alleviate the cognitive and behavioral symptoms of a disease, such as memory loss and confusion, without addressing the underlying disease progression.

"[s]" indicates state mandates may apply.

Policy Statement on Leqembi (lecanemab-irmb) for Alzheimer's Disease Efficacy Information[s]

The use of Leqembi (lecanemab-irmb) is considered unproven and therefore not medically necessary for the treatment of Alzheimer's disease or any other indication, as the available evidence is insufficient to demonstrate clinically meaningful benefit that outweighs potential risks.

- The CLARITY AD trial (NCT03887455) demonstrated a statistically significant 27% slowing of cognitive decline, as measured by the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB), with a mean difference of -0.45 (95% CI: -0.67 to -0.23) points between Leqembi (lecanemab-irmb) and placebo over 18 months. Secondary outcomes, including changes in ADAS-Cog14 and ADCS-MCI-ADL, also favored Leqembi (lecanemab-irmb) over placebo.

    - Leqembi (lecanemab-irmb) reduced amyloid-beta plaque burden significantly, with a mean reduction of -55.48 centiloids compared to +3.64 centiloids for placebo.
    - The absolute difference in CDR-SB scores between Leqembi (lecanemab-irmb) and placebo (-0.45 points) is modest and of uncertain clinical significance, particularly when weighed against the progressive nature of Alzheimer's disease and the limited impact on functional outcomes. The CDR-SB is an 18-point scale, and the minimally clinically important difference (MCID) remains clinically debated though several sources have stated the MCID for MCI due to AD or mild AD dementia would be 0.98-1.63, 1-2, or 1-2.5 points. Even the most conservative threshold for MCID was not met in the CLARITY AD trial.
    - Changes in the secondary outcome for the Alzheimer's Disease Assessment Scale, Cognitive Subscale (ADAS-Cog14), did not meet their predetermined MCID as well, despite being statistically significant. The difference in mean change between Leqembi (lecanemab-irmb) and placebo at the end of the study was -1.44 (95%CI: -2.27 to -0.61), demonstrating a 26% slowing of decline. Several studies have identified an MCID for the ADAS-Cog14 of at least 2 to 5 points.
    - Similar results were found in the phase 2b proof-of-concept study (NCT01767311), which failed to find a statistically significant difference at 12 months on the AD Composite score (ADCOMS); however, at 18-months there was a significant reduction in brain amyloid and significant reduction in the ADCOM compared to the placebo.
    - Long-term outcomes, such as the impact on quality of life, caregiver burden, and overall disease progression, remain unclear.
- On-going studies (pending results):
    - An open-label study (NCT06384573) assessing the safety and efficacy of Leqembi (lecanemab-irmb) in those with dominantly inherited Alzheimer's disease mutations (previously treated with gantenerumab) without symptoms of dementia has begun (active, not recruiting, n=43).
    - A prospective cohort study (NCT05925621) is aiming to create a patient registry assessing the safety, efficacy and timeline of clinical benefit in those on Leqembi (lecanemab-irmb) (recruiting stage).
    - A randomized, placebo-controlled, double-blind, parallel group 18-month study (NCT03887455), followed by an open-label extension, assessing the safety and efficacy of Leqembi (lecanemab-irmb) (intravenous and subcutaneous) in those with MCI or mild AD dementia (active, not recruiting, n=1906)
    - A phase 1 intervention study (NCT06992804) on the addition of near-infrared light therapy in addition to Leqembi (lecanemab-irmb) in those with mild AD (recruiting phase).
    - A placebo-controlled, double-blind, parallel treatment 216 week study (NCT04468659) assessing the safety and efficacy of those with early preclinical AD and intermediate amyloid levels (active, not recruiting, n=1400 estimated).

    - An anti-amyloid therapy registry (NCT05999084) with a goal of assessing real-world population health outcomes (recruiting phase).
    - A Phase ⅔ multicenter randomized, double-blind, placebo-controlled trial (NCT05269394) assessing the safety, efficacy of dominantly inherited AD in those without symptoms of dementia (active, not recruiting, n=197).
    - A safety and feasibility study (NCT05469009) of combining Leqembi (lecanemab-irmb) with blood brain barrier opening Exablate Model 4000 Type 2 (active, not recruiting, n=15).
    - An observation study (NCT07152418) to assess the impact of Leqembi (lecanemab-irmb) in those who progress to moderate stage AD dementia compared to those receiving conventional dementia care (not yet recruiting, n=120 estimated).
    - A real-world observational study (NCT06883019) of those with early onset AD dementia in those <65 years with a family history of AD (recruiting phase, n=114 estimated).
    - A single-arm real-world study (NCT07034222) of the safety and efficacy of Leqembi (lecanemab-irmb) in those with early AD (active, not recruiting).
    - A phase 2/3 multicenter, randomized, double-blind, placebo-controlled study (NCT01760005) of potentially disease modifying therapies (including Leqembi [lecanemab]) in those with dominantly inherited AD.
- Safety Considerations
    - Amyloid-Related Imaging Abnormalities (ARIA), including ARIA-E (edema) and ARIA-H (hemorrhage), was observed in 21% of patients in the CLARITY AD trial, with symptomatic ARIA occurring in 3% of patients. Serious adverse events, including intracerebral hemorrhage, were reported in 0.7% of patients.
        - Risk of ARIA is significantly higher in ApoE ε4 homozygotes, with 45% of homozygotes experiencing ARIA compared to 19% of heterozygotes and 13% of noncarriers.
    - Infusion-related reactions were reported in 26% of patients, with most occurring during the first infusion. Symptoms included fever, chills, nausea, and hypotension.
    - Fatal intracerebral hemorrhage events have been reported in a small number of patients, particularly those on anticoagulants or with risk factors for cerebral amyloid angiopathy.
    - Leqembi (lecanemab-irmb) requires intensive safety monitoring, including baseline and periodic MRIs to detect ARIA, which may limit its feasibility in routine clinical practice.
- Guidelines/Position Statements:
    - While Leqembi (lecanemab-irmb) has received FDA traditional approval, professional guidelines have not yet broadly endorsed its routine use. The Alzheimer's Disease and Related Disorders Therapeutics Work Group has issued appropriate use recommendations, but broader consensus on its role in clinical practice is still evolving.
    - In August 2024 the National Institute for Health and Care Excellence (NICE) guidelines recommended against the use of Leqembi (lecanemab-irmb) in those with AD. They cite that the cost of the medication is too large to justify the small benefits seen with Leqembi.

- The European Medicines Association (EMA) recommends the use of Leqembi (lecanemab-irmb) for those with AD.
- The Alzheimer's Association published an Appropriate Use Recommendations that highlights who should and should not be considered for administration of Leqembi (lecanemab-irmb).

Medical Necessity Criteria for Leqembi (lecanemab-irmb) for Alzheimer's Disease[s]

Leqembi (lecanemab-irmb) is considered unproven and therefore not medically necessary for any indication, including for the treatment of Alzheimer's disease.

Experimental or Investigational or Unproven / Not Medically Necessary[s]

Leqembi (lecanemab-irmb) for any other indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, unproven, or not medically necessary. Non-covered indications include, but are not limited to, the following:

- The treatment of Alzheimer's disease, including:
  - Mild cognitive impairment or mild dementia stage of the disease.
  - Moderate to severe Alzheimer's disease or other stages of dementia.
- Treatment of other neurodegenerative disorders or cognitive impairments unrelated to Alzheimer's disease.
- Prophylactic or preventive treatment in individuals without Alzheimer's disease or at risk for developing Alzheimer's disease.
- Use in combination with other experimental or investigational therapies for Alzheimer's disease or other cognitive disorders.

While clinical trials have demonstrated some potential for slowing cognitive decline in patients with mild cognitive impairment (MCI) or mild dementia due to Alzheimer's disease, the overall clinical utility of Leqembi (lecanemab-irmb) remains uncertain. This determination is based on the above clinical findings summarized in the Policy Statement on Leqembi (lecanemab-irmb) for Alzheimer's Disease Efficacy Information.

The Plan will continue to monitor emerging evidence, including long-term data from ongoing clinical trials, real-world evidence from the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET), and updated guidance from professional organizations. Until such evidence is available, healthcare providers and members are encouraged to explore alternative treatment options with established efficacy and safety profiles.

Applicable Billing Codes

Table 1	
CPT/HCPCS Codes considered experimental, investigational, unproven, or not medically necessary:	
Code	*Description*
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96366	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)
J0174	Injection, lecanemab-irmb, 1mg

Table 2	
ICD-10 diagnosis codes considered experimental, investigational, unproven, or not medically necessary with Table 1 (CPT/HCPCS) codes:	
Code	*Description*
G30	Alzheimer's disease
G30.0	Alzheimer's disease with early onset
G30.1	Alzheimer's disease with late onset
G30.8	Other Alzheimer's disease
G30.9	Alzheimer's disease, unspecified
G31.84	mild cognitive impairment
F00	Dementia in Alzheimer's disease
F00.0	Dementia in Alzheimer's disease with early onset
F00.1	Dementia in Alzheimer's disease with late onset
F00.2	Dementia in Alzheimer's disease, atypical or mixed type
F00.9	Dementia in Alzheimer's disease, unspecified
F01	Vascular dementia
F01.50	Vascular dementia without behavioral disturbance
F01.51	Vascular dementia with behavioral disturbance
F02	Dementia in other diseases classified elsewhere
F02.80	Dementia in other diseases classified elsewhere without behavioral disturbance
F02.81	Dementia in other diseases classified elsewhere with behavioral disturbance

Table 2	
ICD-10 diagnosis codes considered experimental, investigational, unproven, or not medically necessary with Table 1 (CPT/HCPCS) codes:	
F03	Unspecified dementia
F03.90	Unspecified dementia without behavioral disturbance
F03.91	Unspecified dementia with behavioral disturbance
F05	Delirium due to known physiological condition

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