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Lecanemab-irmb

Table of Contents
Coverage
Policy Guidelines
Description
Rationale
Coding
References
Policy History

Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

EXCEPTION: For **Illinois** only: Effective July 1, 2025, PA 103-0975, 5ILCS 375/6.11D, SB3318 Alzheimer Treatment, requires the State Employees Group Insurance Program to provide coverage for all medically necessary FDA-approved treatments or medications prescribed to slow the progression of Alzheimer's Disease or another related dementia, as determined by a physician licensed to practice medicine in all its branches. Coverage for all FDA-approved treatments or medications prescribed to slow the progression of Alzheimer's Disease or another related dementia shall not be subject to step therapy. Any diagnostic testing necessary for a physician to determine appropriate use of these treatments or medications shall be covered by the State Employees Group Insurance Program.

Coverage

Lecanemab-irmb (Leqembi®) **may be considered medically necessary** for the treatment of Alzheimer's Disease (AD) when **ALL** the following criteria are met:

- Individual is aged 50 years or older; **AND**
- Individual has mild cognitive impairment due to AD or mild AD dementia; **AND**
- Individual has positive amyloid load as indicated by one of the following:
  - Positron emission tomography (PET) assessment of imaging agent uptake into brain; or
  - Cerebrospinal fluid (CSF) assessment of amyloid β (Aβ1-42); **AND**
- Individual has a baseline brain magnetic resonance imaging (MRI) prior to initiating treatment; **AND**
- Individual must have one of the following scores at baseline on any of the following assessment tools:
  - Clinical Dementia Rating-Global Score (CDR-GS) of 0.5 or 1; or
  - Mini-Mental Status Examination (MMSE) score of 22-30; **AND**

Lecanemab-irmb (Leqembi®) **is considered experimental, investigational and/or unproven** for all other non-Food and Drug Administration approved indications.

Policy Guidelines

None.

Description

Alzheimer's Disease

Alzheimer's disease (AD) is a fatal neurodegenerative disease that causes progressive loss in memory, language, and thinking, with the eventual loss of ability to perform social and functional activities in daily life. Survival after a diagnosis of dementia due to AD generally

ranges between 4 and 8 years; however, life expectancy can be influenced by other factors, such as comorbid medical conditions. It is estimated that 6.9 million Americans aged 65 and older are currently living with AD dementia, and the number is projected to reach over 13.8 million by 2060. (2)

Pathophysiology

Brain amyloid deposition is a marker of AD pathology. The accumulation of the protein fragment beta-amyloid into clumps (called beta-amyloid plaques) outside neurons and the accumulation of an abnormal form of the protein tau (called tau tangles) inside neurons are two of several brain changes associated with Alzheimer's disease. Beta-amyloid and tau accumulation is followed by damage to and destruction of neurons (called neurodegeneration) and other brain cells. Neurodegeneration, along with beta-amyloid and tau accumulation, is a key feature of Alzheimer's disease. These changes in the brain result in widespread neurodegeneration and cell death, and ultimately cause the clinical signs and symptoms of dementia. (3, 4)

Salient known risk factors for AD are older age, genetics, and family history. Of these, increasing age has the largest known impact on risk of developing AD. While several genes have been found to increase the risk of AD, the ε4 allele of the apolipoprotein E (ApoE) gene is the strongest known genetic risk factor. (5, 6) Having a single copy of the gene is associated with a 2- to 3-fold increase in developing AD while 2 copies of the gene may increase risk of AD by as much as 15 times. (7) Approximately two-thirds of pathology-confirmed AD cases are ε4 positive (homozygous or heterozygous), compared with about 15% to 20% of the general population. (6) Autosomal dominant genetic mutations are estimated to account for less than 1% of AD cases. (8) The pathophysiological changes and clinical manifestations of AD are progressive and occur along a continuum, and accumulation of amyloid beta may begin 20 years or more before symptoms arise. (9)

The National Institute on Aging-Alzheimer's Association (NIA-AA) 2011 guidelines set clinical criteria for mild cognitive impairment (MCI) and dementia. (11, 12) Mild cognitive impairment lies between the cognitive changes of normal aging and dementia. Individuals with MCI are at increased risk of developing dementia (whether from AD or another etiology), but many do not progress to dementia, and some get better. Dementia is a syndrome involving cognitive and behavioral impairment in an otherwise alert patient, due to a number of neurological diseases, alone or combined. It is not a specific cause or disease process itself. The impairment must involve a minimum of 2 domains (memory, reasoning, visuospatial abilities, language or personality behaviors), impact daily functioning, represent a decline from previous levels of functioning, not be explainable by delirium (a temporary state of mental confusion and fluctuating consciousness from various causes) or a major psychiatric disorder, and be objectively documented by a "bedside" mental status exam (e.g., the mini-mental status exam) or neuropsychological testing. (12) These guidelines describe core clinical criteria for "all-cause" dementia and "probable AD" dementia. Briefly, "probable AD" dementia must first meet the criteria for "all-cause" dementia. Additionally, there must be: (a) insidious onset; (b) documented worsening of cognition; (c) exclusion of major concomitant cerebrovascular

disease (as most individuals with AD have some level of this as well); and (d) exclusion of alternative diagnoses (e.g., dementia with Lewy bodies, behavioral variant frontotemporal dementia, progressive aphasia, or other neurological disease associated with dementia). A clinical diagnosis of "possible AD" dementia would meet the criteria for "probable AD" with the exception of having an "atypical course" (e.g., sudden rather than insidious onset) or an "etiologically mixed presentation."

In 2024, NIA-AA updated their "numeric clinical staging scheme" (Table 1) that avoids traditional syndromal labels and is applicable for only those in the Alzheimer continuum. (13) This staging scheme reflects the sequential evolution of AD from an initial stage characterized by the appearance of abnormal AD biomarkers in asymptomatic individuals. The biological definition of AD is consistent with the distinction between a disease and an illness. A disease is a pathogenic condition, while the term illness denotes signs and symptoms that result from the disease. For individuals with biologically confirmed AD, we believe that numeric staging provides a clarifying framework for categorizing the clinical continuum of AD. The term prodromal AD has been used to denote individuals with abnormal AD biomarkers who have clinically evident impairment that falls short of dementia. As biomarker abnormalities progress, the earliest subtle symptoms become detectable. Further progression of biomarker abnormalities is accompanied by progressive worsening of cognitive symptoms, culminating in dementia. These criteria are not intended to provide step-by-step clinical practice guidelines for clinical workflow or specific treatment protocols. Instead, they serve as general principles to inform diagnosis and staging of AD that reflect current science. This numeric staging scheme is very similar to the system for staging AD outlined in the Food and Drug Administration (FDA) guidance for conduct of clinical trials in early AD. (10)

Current Treatment

Current treatment goals for patients with AD are often directed to maintain quality of life, treat cognitive symptoms, and manage behavioral and psychological symptoms of dementia. Treatment remains largely supportive, including creation and implementation of individualized dementia care plans, caregiver education and support, care navigation, care coordination, and referral to community-based organizations for services (e.g., adult day care, caregiver training). (14) Non-pharmacologic treatments include physical activity (15, 16) as well as behavioral strategies to ameliorate neuropsychiatric symptoms (e.g., agitation, delusions, disinhibition), and problem behaviors (e.g., resistance to care, hoarding, obsessive-compulsive behaviors). (17) Currently, FDA-approved drugs for AD include cholinesterase inhibitors, donepezil, rivastigmine, and galantamine, and the N-methyl-D-aspartate antagonist, memantine. Cholinesterase inhibitors are indicated in mild, moderate, and severe AD, while memantine is approved for moderate-to-severe AD. These drugs, either alone or in combination, focus on managing cognitive and functional symptoms of the disease and have not been shown to alter disease trajectory. The evidence for efficacy is limited and these agents are associated with significant side effects. (18, 19)

Table 1. National Institute on Aging-Alzheimer's Association Numerical Clinical Staging for Individuals in the Alzheimer Continuum[a]

Stage	Severity	Clinical Features
Stage 0	Asymptomatic, deterministic gene	• No evidence of clinical change. • Biomarkers in normal range.
Stage 1	Asymptomatic, biomarker evidence only	• Performance within expected range on objective cognitive tests. • No evidence of recent cognitive decline or new symptoms.
Stage 2	Transitional decline: mild detectable change, but minimal impact on daily function	• Normal performance within expected range on objective cognitive tests. • May be documented by evidence of subtle decline on longitudinal cognitive testing, which may involve memory or other cognitive domains but performance still within normal range. • May be documented through subjective report of cognitive decline. • May be documented with recent onset change in mood, anxiety, motivation not explained by life events. • Remains fully independent with no or minimal functional impact on ADLs.
Stage 3	Cognitive impairment with early functional impact	• Performance in the impaired/abnormal range on objective cognitive tests. • Evidence of decline from baseline, documented by the individual's report or by an observer's (e.g., study partner) report or by change on longitudinal. Cognitive testing or neurobehavioral assessments. • Performs daily life activities independently, but cognitive difficulty may result in detectable functional impact on complex activities of daily life (i.e., may take more time or be less efficient but still can complete-either self-reported or corroborated.
Stage 4	Dementia with mild functional impairment	• Progressive cognitive and mild functional impairment on instrumental ADLs, with independence in basic ADLs.
Stage 5	Dementia with moderate functional impairment	• Progressive cognitive and moderate functional impairment on ADLs requiring assistance.
Stage 6	Dementia with severe functional impairment	• Progressive cognitive and functional impairment, and complete dependence for basic ADLs.

[a] Individuals with Down syndrome may not be fully independent even in stage 0 because of underlying intellectual disability. In these individuals, decline in functional independence from baseline may be a more appropriate indicator of stage.
ADL: activities of daily living.

Lecanemab-irmb (Leqembi®)
Lecanemab-irmb is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble (protofibril) and insoluble forms of amyloid beta (Aβ). Lecanemab is believed to reduce the number of amyloid plaques present in the brain, potentially slowing neurodegeneration and disease progression. (1)

Although there are no labeled contraindications, there are warnings and precautions which include amyloid related imaging abnormalities (ARIA) and infusion-related reactions. Monoclonal antibodies directed against aggregated forms of beta amyloid can cause ARIA, characterized as ARIA with edema (ARIA-E), which can be observed on magnetic resonance imaging (MRI) as brain edema or sulcal effusions, and ARIA with hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis. ARIA-H can occur spontaneously in patients with AD. ARIA-H associated with monoclonal antibodies directed against aggregated forms of beta amyloid generally occurs in association with an occurrence of ARIA-E. ARIA-H of any cause and ARIA-E can occur together. ARIA is usually asymptomatic, although serious and life-threatening events, including seizure and status epilepticus, can occur. When present, reported symptoms associated with ARIA may include headache, confusion, visual changes, dizziness, nausea, and gait difficulty. Focal neurologic deficits may also occur. Symptoms associated with ARIA usually resolve over time. The risk of ARIA, including symptomatic and serious ARIA, is increased in apolipoprotein E ε4 (ApoE ε4) homozygotes. In addition to ARIA, intracerebral hemorrhages greater than 1 cm in diameter have occurred in patients treated with Leqembi. (1)

Regulatory Status
In January 2023, lecanemab-irmb (Leqembi®, Eisai, Inc.) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of Alzheimer's disease. This indication was approved under accelerated approval based on the reduction in amyloid beta plaques observed in patients treated with lecanemab-irmb. In July 2023, the FDA provided full approval to Leqembi for the treatment of Alzheimer's disease in patients with mild cognitive impairment or mild dementia state of disease. (1)

Rationale

This policy is based on the U.S. Food and Drug Administration (FDA) labeled indications for lecanemab-irmb (Leqembi®).

Lecanemab-irmb (Leqembi®) (1)
The efficacy of Leqembi was evaluated in two double-blind, placebo-controlled, parallel-group, randomized studies (Study 1, NCT01767311; Study 2, NCT03887455) in patients with

Alzheimer's disease (patients with confirmed presence of amyloid pathology and mild cognitive impairment [64% of patients in Study 1; 62% of patients in Study 2] or mild dementia stage of disease [36% of patients in Study 1; 38% of patients in Study 2], consistent with Stage 3 and Stage 4 Alzheimer's disease). In both studies, patients were enrolled with a Clinical Dementia Rating (CDR) global score of 0.5 or 1.0 and a Memory Box score of 0.5 or greater. All patients had a Mini-Mental State Examination (MMSE) score of ≥22 and ≤30 and had objective impairment in episodic memory as indicated by at least 1 standard deviation below age-adjusted mean in the Wechsler-Memory Scale-IV Logical Memory II (subscale) (WMS-IV LMII). Patients were enrolled with or without concomitant approved therapies (cholinesterase inhibitors and the N-methyl-D-aspartate antagonist memantine) for Alzheimer's disease. Patients in each study could enroll in an optional, long-term extension.

Study 1

In Study 1, 856 patients were randomized to receive one of 5 doses (161 of which were randomized to the recommended dosing regimen of 10 mg/kg every two weeks) of Leqembi or placebo (n=247). Of the total number of patients randomized, 71.4% were apolipoprotein E4 (ApoE4) carriers and 28.6% were ApoE4 non-carriers. During the study the protocol was amended to no longer randomize ApoE4 carriers to the 10 mg/kg every two weeks dose arm. ApoE4 carriers who had been receiving Leqembi 10 mg/kg every two weeks for 6 months or less were discontinued from study drug. As a result, in the Leqembi 10 mg/kg every two weeks arm, 30.3% of patients were ApoE4 carriers and 69.7% were ApoE4 non-carriers. At baseline, the mean age of randomized patients was 71 years, with a range of 50 to 90 years. Fifty percent of patients were male and 90% were White.

In Study 1, a subgroup of 315 patients were enrolled in the amyloid PET substudy; of these, 277 were evaluated at week 79. Results from the amyloid beta PET substudy are described in Table 2. Plasma biomarkers are described in Table 2.

Table 2. Results of Amyloid Beta PET in Study 1

Biomarker Endpoints	**Leqembi 10 mg/kg every two weeks**	**Placebo**
Amyloid Beta PET Composite SUVr	N=44	N=98
Mean baseline	1.373	1.402
Adjusted mean change from baseline at Week 79 Difference from placebo	-0.306 -0.310 (p<0.001)[1]	0.004
Amyloid Beta PET Centiloid	N=44	N=98
Mean Baseline	78.0	84.8
Adjusted mean change from baseline at Week 79 Difference from placebo	-72.5 -73.5 (p<0.001)[1]	1.0

N is the number of patients with baseline value; mg/kg: milligrams per kilogram; PET: positron emission tomography; SUVr: Standard Uptake Value ratio.

[1] P-values were not statistically controlled for multiple comparisons.

The primary endpoint was change from baseline on a weighted composite score consisting of selected items from the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB), MMSE, and Alzheimer Disease Assessment Scale – Cognitive Subscale 14 (ADAS-Cog 14) at Week 53. Leqembi had a 64% likelihood of 25% or greater slowing of progression on the primary endpoint relative to placebo at Week 53, which did not meet the prespecified success criterion of 80%.

Key secondary efficacy endpoints included the change from baseline in amyloid PET SUVR composite at Week 79 and change from baseline in the CDR-SB and ADAS-Cog14 at Week 79. Results for clinical assessments showed less change from baseline in CDR-SB and ADAS-Cog 14 scores at Week 79 in the Leqembi group than in patients on placebo (CDR-SB: -0.40 [26%], 90% CI [-0.82, 0.03]; ADAS-Cog 14: -2.31 [47%], 90% CI [-3.91, -0.72]).

After the 79-week double-blind, placebo-controlled period of Study 1, patients could enroll in an open-label extension period for up to 260 weeks, which was initiated after a gap period (range, 9 to 59 months; mean, 24 months) off treatment.

Study 2

In Study 2, 1795 patients were enrolled and randomized 1:1 to receive Leqembi 10 mg/kg or placebo once every 2 weeks. Of the total number of patients randomized, 69% were ApoE ε4 carriers and 31% were ApoE ε4 non-carriers. Overall median age of patients was 72 years, with a range of 50 to 90 years. Fifty-two percent were women, and 1381 (77%) were White, 303 (17%) were Asian, and 47 (3%) were Black.

The randomization was stratified according to clinical subgroup (mild cognitive impairment or mild dementia stage of the disease); the presence or absence of concomitant approved therapies for Alzheimer's disease at baseline (cholinesterase inhibitors and the N-methyl-D-aspartate antagonist memantine); ApoE ε4 carrier status; and geographical region.

The primary efficacy outcome was change from baseline at 18 months in the CDR-SB. Key secondary endpoints included change from baseline at 18 months for the following measures: amyloid Positron Emission Tomography (PET) using Centiloids, ADAS-Cog14, and Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS MCI-ADL).

Leqembi treatment met the primary endpoint and reduced clinical decline on the global cognitive and functional scale, CDR-SB, compared with placebo at 18 months (-0.45 [-27%], $p<0.0001$).

Statistically significant differences ($p<0.01$) between treatment groups were also seen in the results for ADAS-Cog14 and ADCS MCI-ADL at 18 months as presented in Table 3.

Both ApoE ε4 carriers and ApoE ε4 noncarriers showed statistically significant treatment differences for the primary endpoint and all secondary endpoints. In an exploratory subgroup

analysis of ApoE ε4 homozygotes, which represented 15% of the trial population, a treatment effect was not observed with Leqembi treatment on the primary endpoint, CDR-SB, compared to placebo, although treatment effects that favored Leqembi were observed for the secondary clinical endpoints, ADAS-Cog 14 and ADCS MCI-ADL. Treatment effects on disease-relevant biomarkers (amyloid beta PET, plasma Aβ42/40 ratio, plasma p-tau 181) also favored Leqembi in the ApoE ε4 homozygous subgroup.

Starting at six months, across all time points, Leqembi treatment showed statistically significant changes in the primary and all key secondary endpoints from baseline compared to placebo.

Table 3. Results for CDR-SB, ADAS-Cog14, and ADCS MCI-ADL in Study 2

Clinical Endpoints	Leqembi 10 mg/kg Every Two Weeks	Placebo
CDR-SB	N=859	N=875
Mean baseline	3.17	3.22
Adjusted mean change from baseline at 18 months (%) Difference from placebo	1.21 -0.45 (-27%) (p<0.0001)	1.66
ADAS-Cog14	N=854	N=872
Mean baseline	24.45	24.37
Adjusted mean change from baseline at 18 months (%) Difference from placebo	4.140 -1.442 (-26%) (p=0.00065)	5.581
ADCS MCI-ADL	N=783	N=796
Mean baseline	41.2	40.9
Adjusted mean change from baseline at 18 months Difference from placebo	-3.5 (-37%) 2.0 (p<0.0001)	-5.5

CDR-SB: Clinical Dementia Rating scale Sum of Boxes; ADAS-Cog14: Alzheimer Disease Assessment Scale – Cognitive Subscale 14; ADCS MCI-ADL: Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; mg/kg: milligram per kilogram.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J0174

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

U.S. Food and Drug Administration Label:

1. U.S. Food and Drug Administration, Drugs@FDA. Highlights of Prescribing Information: Leqembi® (Revised 1/2025). Available at <https://www.accessdata.fda.gov> (accessed June 10, 2025).

Other:

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
08/15/2025	Document updated with literature review. Revised coverage to be in alignment with the current FDA label for Lecanemab-irmb (Leqembi®). Lecanemab-irmb (Leqembi®) is considered experimental, investigational and/or unproven for all other non-FDA approved indications. Added references 12 and 19; others updated.

04/15/2025	Document updated with literature review. The following change was made to Coverage: Under Continuation of Therapy; the statement “Magnetic resonance imaging (MRI) is obtained prior to the 5th, 7th, and 14th infusions to monitor for amyloid related imaging abnormalities (ARIA).” was changed to “Routine magnetic resonance imaging (MRI) is performed to monitor for amyloid related imaging abnormalities (ARIA).”Reference 11 added; others updated.
04/01/2024	Reviewed. No changes.
08/15/2023	Document updated with literature review. The following changes were made to Coverage: Added medically necessary coverage for Lecanemab-irmb (Leqembi®) when specific criteria are met for both initial therapy and continuation therapy. Lecanemab-irmb (Leqembi®) is experimental, investigational and/or unproven for all other indications. References revised.
06/01/2023	New medical document. Lecanemab-irmb (Leqembi™) for the treatment of Alzheimer’s disease in individuals with mild cognitive impairment or mild dementia stage of disease is considered not medically necessary as a clinical benefit has not been established. Lecanemab-irmb (Leqembi™) for the treatment of all other indications is considered experimental, investigational and/or unproven.