Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (for Louisiana Only)

Policy Number: CSLA2023D0108A
Effective Date: TBD

Instructions for Use

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Application

This Medical Benefit Drug Policy only applies to the state of Louisiana. This Medical Benefit Drug Policy does not apply for **Aduhelm**; refer to the state's Medicaid clinical policy for Aduhelm.

Coverage Rationale

Leqembi (lecanemab-irmb) is covered for the treatment of Alzheimer's disease (AD) when all of the following criteria are met:

- Diagnosis of mild cognitive impairment (MCI) due to AD or mild AD dementia; **and**
- Patient has confirmed presence of amyloid beta pathology consistent with AD; **and**
- Consistent with the Centers for Medicare & Medicaid Services (CMS) decision memo (CMS Final Decision Memo - *Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (CAG-00460N)*) the patient will be receiving Leqembi through an FDA randomized controlled trial conducted under an investigational new drug (IND) application.[34]

*The Centers for Medicare & Medicaid Services (CMS) covers Food and Drug Administration (FDA) approved monoclonal antibodies directed against amyloid for the treatment of Alzheimer's disease (AD) when furnished under coverage with evidence development (CED). *Approved CED studies are posted on the CMS Coverage with Evidence Development webpage (see:* Coverage with Evidence Development | CMS)

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The

inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J3590	Injection, lecanemab-irmb, 10 mg

Diagnosis Code	Description
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

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.[2]

AD is characterized by deposition of 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.

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.[4]

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.[5]

Age of AD onset:[6]

- 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%).[7]

- 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:[8]

- 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 as a 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.[9,30] 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.[16]

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

CDR-SB Score	Disease Severity
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.[9,10,17,30]

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.[9,31]

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.[32]

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:[10]

- 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.[29]

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	Numeric Clinical Staging—Applicable Only to Individuals in the Alzheimer's Continuum
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.
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.

Despite the existence of several FDA-approved therapies for AD, there is an unmet medical need for treatments that are intended to address the biological basis of AD. Currently approved treatments do not target the underlying pathology of AD. Cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) and the NMDA-antagonist, memantine, are the only FDA-approved and guideline-recommended treatments for AD dementia.[11] The majority of patients with newly diagnosed AD should be offered a trial of a cholinesterase inhibitor for symptomatic treatment of cognition and global functioning. However, the degree of expected benefit is modest, and therapy should only be continued in patients who appear to be benefiting.[10]

Lecanemab is a humanized IgG1 monoclonal antibody that binds to soluble Aβ aggregates (oligomers and protofibrils) with high selectivity over monomer and insoluble fibrils., which have been shown to be more toxic to neurons than monomers or insoluble fibrils.[37,38]

Clinical Evidence

Multiple investigational anti-Aβ antibodies have been developed with the goal of either reducing production of Aβ or lowering levels of aggregated Aβ present in the brain, the latter of which has been the most pursued approach. Many of these investigational drugs have failed to demonstrate efficacy and/or safety. Some explanations for the failures of previous anti-Aβ antibodies include the following:[12]

- Inclusion of patients in clinical trials without evidence of Aβ pathology
- Unknown or no target engagement prior to initiation of Phase 3 study (i.e., poor selectivity of drug for neurotoxic Aβ)
- Lack of robust and sustained inhibition of soluble Aβ oligomers
- Use of subtherapeutic doses (possibly due to decreased brain penetration)
- Inclusion of patients at later stages of AD dementia, when significant irreversible neurodegeneration has already occurred

FDA approval for lecanemab was based on Study 201, an 18-month, Phase 2b, double-blind, placebo controlled, multicenter, randomized control trial that evaluated the safety and efficacy of lecanemab. The study aimed to establish the effective dose 90% (ED90), defined as the simplest dose that achieves ≥ 90% of the maximum treatment effect. The primary endpoint was Bayesian analysis of 12-month clinical change on the Alzheimer's Disease Composite Score (ADCOMS) for the ED90 dose, which required an 80% probability of ≥25% clinical reduction in decline versus placebo. Study 201 enrolled 854 were treated to

lecanemab, 609 or placebo, 245. Of the total number of patients randomized, 71.4% were ApoE ε4 carriers and 28.6% were ApoE ε4 non-carriers. During the study, the protocol was amended to no longer randomize ApoE ε4 carriers to the 10 mg/kg every two weeks dose arm. ApoE ε4 carriers who had been receiving lecanemab 10 mg/kg every two weeks for 6 months or less were discontinued from study drug. The primary analysis conducted at Month 12 of treatment indicated that the 10 mg/kg IV biweekly dose (the effective dose) had a 64% probability to be better than placebo by 25% on ADCOMS at 12 months, missing the prespecified 80% probability threshold for the primary outcome.
The results for the Bayesian analysis for reduction of clinical decline at 18 months vs placebo for 10 mg/kg biweekly on ADCOMS (-27%, with 97.7% probability to be superior to placebo), CDR-SB (33%, with 96.4% probability to be superior to placebo), and ADASCog14 (56%, with a 98.8% probability to be superior to placebo) were similar to the results from the corresponding conventional analyses for clinical measures when comparing mean change from baseline and lease squares (LS) mean data.[37]

CLARITY AD was an 18 month, Phase 3, double-blind, placebo-controlled, multicenter, randomized controlled trial that evaluated the safety and efficacy of lecanemab in 1,795 patients with early AD. Participants were randomly assigned in a 1:1 ratio to receive IV lecanemab (10 mg/kg every 2 weeks) or placebo. The primary endpoint was the change from baseline at 18 months in the CDR-SB. Lecanemab demonstrated a statistically significantly reduction in the rate of cognitive decline -27% (difference vs placebo, - 0.27%; CDR-SB = - 0.45 [95% CI, -0.67 to -0.23; p < 0.001]) at 18 months. Furthermore, a slope analysis demonstrated that lecanemab took 5.5 to 6 months more time to achieve the same CDR-SB as placebo at 18 months, indicating a 5.5 to 6 month slowing of progression. Aβ plaque reduction was a secondary endpoint and was studied in a subset of patients (n = 698). The adjusted mean change from baseline at 18 months was -55.48 centiloids in the lecanemab group vs 3.64 centiloids in the placebo group (adjusted mean difference, -59.12 centiloids; 95% CI, -62.64 to -55.60; p < 0.001).[38]

The incidence of ARIA-E with lecanemab was 12.5% vs 1.7% with placebo (symptomatic ARIA-E: 2.8% vs 0% with placebo). The incidence of ARIA-H was 17.0% vs 8.7% with placebo (symptomatic ARIA-H: 0.7% vs 0.2% in placebo group). No deaths due to ARIA were reported due to lecanemab use in CLARITY-AD. In recent months, however, 3 deaths that occurred during the OLE have been reported by multiple news outlets. These deaths are thought to be related to ARIA in patients who had switched from placebo during the core study to lecanemab during the OLE.[39]

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Leqembi (lecanemab-irmb) is an Aβ-targeting antibody 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. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients receiving treatment. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

To monitor for Amyloid Related Imaging Abnormalities (ARIA), a recent (within one year) brain magnetic resonance imaging (MRI) prior to initiating treatment is required for Leqembi. Leqembi recommends MRIs prior to the 5th, 7th, and 14th infusion.

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Policy History/Revision Information

Date	Summary of Changes
TBD	New Medical Benefit Drug Policy

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

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Archived Policy Versions

Effective Date	Policy Number	Policy Title