

Monoclonal Antibodies for the Treatment of Alzheimer's Disease

Policy # 00754

Original Effective Date: 09/13/2021

Current Effective Date: 09/01/2026

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Investigational or experimental services are not covered. This includes any drug, device, procedure, or service provided under the investigational arm of a clinical trial or clinical study. These services are excluded from coverage under benefits.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the use of lecanemab-irmb (Leqembi[®], Leqembi[®] Iqlik[™])[‡] or donanemab-azbt (Kisunla[™])[‡] for the treatment of Alzheimer's disease to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for lecanemab-irmb (Leqembi, Leqembi Iqlik) or donanemab-azbt (Kisunla) will be considered when the following criteria are met:

Initial (12 months)

- Patient is 50-90 years of age; AND
- Patient has a diagnosis of mild cognitive impairment (MCI) due to Alzheimer's disease (Clinical Stage 3) or mild Alzheimer's dementia (Clinical Stage 4); AND
- Patient meets ONE of the following
 - Patient must have one or more of the following scores at baseline on any of the following assessment tools:
 - Clinical Dementia Rating (CDR)- Global Score of 0.5-1.0 OR CDR-SB less than 7
 - FAST- stage less than 5
 - Montreal Cognitive Assessment (MoCA) score of greater than or equal to 17; OR
 - Patient has completed a cognitive battery (MMSE + MoCA + formal neuropsychological testing) demonstrating MCI or mild dementia; AND

Monoclonal Antibodies for the Treatment of Alzheimer's Disease

Policy # 00754

Original Effective Date: 09/13/2021

Current Effective Date: 09/01/2026

- Patient must have the presence of amyloid beta pathology as confirmed by one of the following (must submit a copy of medical imaging results or diagnostic immunoassay):
 - Amyloid positron emission tomography (PET) confirming the presence of amyloid pathology (global centiloid greater than 25); AND
 - If Cerebrospinal fluid (CSF) assay performed, there is evidence of high concordance with amyloid PET scan to assess the presence of amyloid deposition AND
- Provider submits documentation of shared decision making addressing benefit, ARIA risk, risks associated with apolipoprotein E (*ApoE*) $\epsilon 4/\epsilon 4$ homozygous state, and monitoring burden; AND
- Patient has no contraindication to magnetic resonance image (MRI); AND
- MRI completed within the previous 12 months does NOT show:
 - Evidence of a non-Alzheimer's disease dementia; OR
 - Findings consistent with cerebral amyloid angiopathy (CAA), (i.e., more than 2 lobar cerebral microbleeds, lobar intracranial hemorrhage, or cortical superficial siderosis [focal or disseminated]); OR
 - Macrohemorrhage; OR
 - Evidence of severe white-matter disease and vasogenic edema; AND
- Patient does not have a history of ANY of the following:
 - Brain aneurysm or other vascular malformation (excluding aneurysms diagnosed more than 5 years ago that have remained stable on imaging and received neurosurgical clearance); OR
 - Brain tumor; OR
 - CNS infection; OR
 - Down syndrome; OR
 - Active malignancy; OR
 - Uncontrolled seizures within past 6 months; OR
 - Intracranial shunts; OR
 - Prior craniotomy/ intracranial surgery (excluding procedures greater than 5 years ago for conditions that have remained clinically and radiographically stable and with neurosurgical clearance); AND
- Patient does NOT have any of the following:
 - Concurrent neurological condition(s) other than MCI due to Alzheimer's Disease (AD) contributing to cognitive impairment, including but not limited to symptoms related to another neurological or psychiatric condition (e.g., frontotemporal lobar degeneration, Lewy body dementia, Parkinson's disease, vitamin B12 deficiency, etc.); OR
 - History of stroke or transient ischemic attacks prior to initiating treatment; OR
 - Bleeding disorder that is not under adequate control (i.e., platelet count less than 50,000 and international normalized ratio [INR] greater than 1.5); OR
 - Immunologic disorder requiring treatment with disease modifying anti-rheumatic drugs (DMARDs) (3 months washout is required after stopping DMARDs);
Note that concurrent use with Otezla or hydroxychloroquine is permitted; AND

Monoclonal Antibodies for the Treatment of Alzheimer's Disease

Policy # 00754

Original Effective Date: 09/13/2021

Current Effective Date: 09/01/2026

- Patient is not receiving anticoagulant therapy (Note: anticoagulant therapy includes warfarin and the direct oral anticoagulants such as apixaban [Eliquis[®]][‡], rivaroxaban [Xarelto[®]][‡], and dabigatran [Pradaxa[®]][‡]. Antiplatelet agents such as aspirin and clopidogrel are not considered exclusions.); AND
- Anti-amyloid antibodies will not be used in combination with each other; AND
- Dose and monitoring are in accordance with the U.S. Food and Drug Administration (FDA) approved prescribing label (see Policy Guidelines).

Continuation (12 months)

- Patient has received an initial authorization for the requested drug; AND
- Patient has not progressed to moderate or severe dementia; AND
- Patient has received MRI monitoring during treatment according to the scheduling recommended in the FDA approved prescribing label to monitor for amyloid-related imaging abnormalities (ARIA) (see Policy Guidelines) which does not show:
 - ARIA-H or recurrent or serious ARIA or an event whose per-label management requires cessation; OR
 - Evidence of significant pathological findings on brain MRI (i.e., findings consistent with cerebral amyloid angiopathy [CAA], brain aneurysm or other vascular malformation, brain tumor, or CNS infection); OR
 - Evidence of stroke; AND
- Patient will continue to be monitored for ARIA or other adverse events according to the labeled recommendations; AND
- Patient has experienced a positive clinical response as evidenced by stabilization or slowing of disease progression as documented by any of the following (Note: repeat assessment tool(s) must be the same tool that was submitted upon initial request):
 - CDR-Global score (i.e., score of 0-1); OR
 - MMSE (i.e., decline of 3 points or less per year and remains between 21-30); OR
 - MoCA (i.e., score of greater than or equal to 16); AND
- If the requested drug is Kisunla, amyloid studies have not shown normalization (e.g., reduction of amyloid plaques to minimal levels on amyloid PET imaging).

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of lecanemab-irmb (Leqembi[®], Leqembi Iqlik) or donanemab-azbt (Kisunla) when the above patient selection criteria are not met to be **not medically necessary**.**

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of lecanemab-irmb (Leqembi, Leqembi Iqlik) or donanemab-azbt (Kisunla) for indications other than the treatment of Alzheimer's disease in the mild cognitive impairment or mild dementia stage of disease or for doses outside of those recommended by the Food and Drug Administration (FDA) to be **investigational**.*

Policy # 00754

Original Effective Date: 09/13/2021

Current Effective Date: 09/01/2026

Policy Guidelines

FDA Approved Dosing

Route of Administration	Dose	Frequency
Leqembi Starting Dosage		
Intravenous (Leqembi)	10 mg/kg	Once every 2 weeks
Subcutaneous (Leqembi Iqlik)	500 mg (two 250 mg injections)	Once every week
Leqembi Maintenance Dosage		
Intravenous (Leqembi)	10 mg/kg	Once every 4 weeks
Subcutaneous (Leqembi Iqlik)	360 mg	Once every week
Kisunla		
Intravenous (Kisunla)	1400 mg*	Once every 4 weeks

*Kisunla dose should be initiated with the following regimen for the first four infusions: 350 mg for infusion 1, 700 mg for infusion 2, 1050 mg for infusion 3, and 1400 mg for infusion 4 and beyond.

ARIA Monitoring Requirements

Drug	FDA-Recommended MRI Schedule
Leqembi	Baseline MRI; then prior to 3 rd , 5 th , 7 th , and 14 th infusions and when clinically warranted based on symptoms.
Kisunla	Baseline MRI; then prior to 2 nd , 3 rd , 4 th , and 7 th doses and when clinically warranted based on symptoms.

Clinical Dementia Rating (CDR) Scale

The CDR is a measure used to stage dementia in the clinical and research setting and is comprised of 75 items related to cognition and function.

- Global Score (CDR-GS) = calculated score that provides an overall rating of dementia severity using six areas—Memory, Orientation, Judgement/Problems Solving, Community Affairs, Home/Hobbies, and Personal Care. The Memory area is considered the primary category within the CDR-GS tool
 - 0 = no dementia/normal
 - 0.5 = questionable cognitive impairment/very mild dementia
 - 1 = mild cognitive impairment/mild dementia
 - 2 = moderate dementia
 - 3 = severe dementia
- Sum of Boxes Score (CDR-SB) = detailed quantitative general index across the six categories
 - 0 = no dementia/normal
 - 0.5 - 4.0 = questionable cognitive impairment
 - 0.5 - 2.0 = questionable impairment
 - 2.5 - 4.0 = very mild dementia
 - 4.5 - 9.0 = mild dementia
 - 9.5 - 15.5 = moderate dementia
 - 16.0 - 18.0 = severe dementia

Policy # 00754

Original Effective Date: 09/13/2021

Current Effective Date: 09/01/2026

Mini Mental State Examination (MMSE)

An 11-question tool used to assess mental status that tests 5 areas of cognitive function- Orientation, Registration, Attention/Calculation, Recall, and Language. Scale is a range from 0 to 30 with 0 being severe dementia and 30 being no dementia.

Montreal Cognitive Assessment (MoCA)

A brief screening tool used to assess mild cognitive impairment that evaluates multiple cognitive domains, including visuospatial/executive function, naming, memory, attention, language, abstraction, delayed recall, and orientation. The total score is added across all cognitive domains and higher scores indicate better cognitive function. One point may be added to the score for individuals with less than or equal to 12 years of education.

- 26 – 30 = normal cognition
- 18 – 25 = mild cognitive impairment
- 10 – 17 = moderate cognitive impairment
- < 10 = severe cognitive impairment

Background/Overview

Leqembi and Kisunla are monoclonal antibodies directed against soluble and insoluble forms of beta-amyloid implicated in the pathogenesis of Alzheimer's disease. According to the prescribing information for both products, the presence of amyloid beta pathology should be confirmed prior to initiating treatment. Leqembi is initially dosed at 10 mg/kg intravenously every two weeks or 500 mg subcutaneously every week. After 18 months of treatment, patients may continue to receive maintenance treatment at a dose of 10 mg/kg IV every 4 weeks or 360 mg SC using the Leqembi Iqlik autoinjector every week. Kisunla is administered intravenously every 4 weeks with the dose titrated over 16 weeks to 1400 mg. The prescribing information for Kisunla indicates that Kisunla dosing could be stopped based on reduction of amyloid plaques to minimal levels on amyloid PET imaging.

Due to the risk of amyloid-related imaging abnormalities, the product labels require a baseline brain magnetic resonance imaging (MRI) prior to initiating treatment. Subsequently, MRI should be repeated prior to the 3rd, 5th, 7th, and 14th infusions of Leqembi and the 2nd, 3rd, 4th, and 7th infusions of Kisunla. Management of ARIA, including dose interruption or discontinuation, should be guided by radiographic severity and clinical symptoms. Testing for apolipoprotein E ε4 (ApoE ε4) genotype should be considered prior to initiation to inform ARIA risk. Additional recommendations are provided in the package inserts for the management of patients with ARIA if it is detected on MRI.

In April 2023, the Institute for Clinical and Economic Review (ICER) published a report assessing the effectiveness and value of Leqembi for Alzheimer's disease. The report concluded, "the net health benefits of lecanemab in participants with early AD (Alzheimer's Disease) may be small or even substantial, but there remains a possibility of net harm from ARIA (amyloid-related imaging abnormalities), we rate treatment with lecanemab in mild cognitive impairment due to AD or mild AD as promising but inconclusive."

Policy # 00754

Original Effective Date: 09/13/2021

Current Effective Date: 09/01/2026

A 2026 Cochrane systematic review of 17 randomized controlled trials (n = 20,342) evaluated amyloid beta–targeting monoclonal antibodies in patients with mild cognitive impairment or mild dementia due to Alzheimer's disease. While these therapies effectively reduce amyloid burden in the brain, the review found that they result in little to no clinically meaningful benefit. Effects on cognitive decline and dementia severity were absent or trivial and fell well below established thresholds for clinical importance, with similarly minimal impact on functional outcomes.

Alzheimer's Disease

Alzheimer's disease 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 Alzheimer's disease generally ranges between 4 and 8 years; however, life expectancy can be influenced by other factors, such as comorbid medical conditions. Approximately 7 million Americans aged 65 and older are currently living with Alzheimer's disease dementia, and the number is projected to reach over 12 million by 2050.

The pathologic hallmarks of Alzheimer's disease are extracellular deposits of beta-amyloid (A- β), referred to as amyloid plaques, and intracellular aggregates of hyperphosphorylated tau in the form of neurofibrillary tangles. There are different forms of amyloid such as plaques, oligomers, and monomers, and the roles of these different forms and how specifically they are pathophysiologically associated with Alzheimer's disease is not well understood. Generally referred to as “amyloid hypothesis”, it is believed that aggregation of A- β oligomers in the brain leads to amyloid plaques which are thought to be the primary driver of the disease process. Amyloid aggregation is thought to precede accumulation of tau pathology and neurodegeneration. These changes in the brain result in widespread neurodegeneration and cell death and ultimately cause the clinical signs and symptoms of dementia.

Salient known risk factors for Alzheimer's disease are older age, genetics, and family history. Of these, increasing age has the largest known impact on risk of developing Alzheimer's disease. While several genes have been found to increase the risk of Alzheimer's disease, the $\epsilon 4$ allele of the apolipoprotein E (*ApoE*) gene is the strongest known genetic risk factor. Having 1 copy of the gene is associated with a 2- to 3-fold increase in developing Alzheimer's disease while 2 copies of the gene may increase risk of Alzheimer's disease by as much as 15 times. Approximately two-thirds of pathology-confirmed Alzheimer disease cases are $\epsilon 4$ positive (homozygous or heterozygous), compared with about 15% to 20% of the general population. Autosomal dominant genetic mutations are estimated to account for less than 1% of Alzheimer's disease cases.

The pathophysiological changes and clinical manifestations of Alzheimer's disease are progressive and occur along a continuum, and accumulation of A- β may begin 20 years or more before symptoms arise. National Institute on Aging-Alzheimer's Association (NIA-AA) have created a “numeric clinical staging scheme” (Table 1) that avoids traditional syndromal labels and is applicable for only those in the Alzheimer continuum. This staging scheme reflects the sequential evolution of Alzheimer's disease from an initial stage characterized by the appearance of abnormal Alzheimer's disease biomarkers in asymptomatic individuals. As biomarker abnormalities progress, the earliest subtle symptoms become detectable. Further progression of biomarker abnormalities is accompanied

Monoclonal Antibodies for the Treatment of Alzheimer's Disease

Policy # 00754

Original Effective Date: 09/13/2021

Current Effective Date: 09/01/2026

by progressive worsening of cognitive symptoms, culminating in dementia. This numeric cognitive staging scheme is not designed to be used in a clinical setting but to be used for interventional trials. This numeric staging scheme is very similar to the categorical system for staging Alzheimer's disease outlined in the Food and Drug Administration (FDA) guidance for industry pertaining to developing drugs for treatment of early Alzheimer's disease.

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

Stage	Severity	Clinical Features
Stage 1	Pre-clinical	• Performance within expected range on objective cognitive tests. • No evidence of recent cognitive decline or new neurobehavioral symptoms
Stage 2	Pre-clinical	• Normal performance within expected range on objective cognitive tests. • Transitional cognitive decline (change from individual baseline within past 1 to 3 years, and persistent for at least 6 months). • Mild neurobehavioral changes may coexist or may be the primary complaint rather than cognitive. • No functional impact on daily life activities.
Stage 3	Mild Cognitive Impairment (MCI) due to Alzheimer's disease	• Performance in the impaired/abnormal range on objective cognitive tests. • Evidence of decline from baseline. • Performs daily life activities independently, but cognitive difficulty may result in detectable but mild functional impact on the more complex activities of daily life.
Stage 4	Mild Dementia	• Substantial progressive cognitive impairment affecting several domains, and/or neurobehavioral disturbance. • 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.

Policy # 00754

Original Effective Date: 09/13/2021

Current Effective Date: 09/01/2026

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.
---------	-----------------	--

Adapted from Table 6, Jack et al (2018)

Many tests are available in the market to detect the underlying core pathology using certain biomarkers in the cerebrospinal fluid (CSF) (e.g., decreased A- β and increased CSF tau protein levels) or on imaging (e.g., amyloid on positron emission tomography [PET] scans). Approved amyloid PET tracers in the US include [^{18}F]-florbetapir, [^{18}F]-flutemetamol and [^{18}F]-florbetaben. In addition, there are several blood-based tests for A- β confirmation that are currently in development. CSF tests and amyloid PET tracers are routinely used in the enrollment of participants in contemporary Alzheimer's disease studies.

Current treatment goals for patients with Alzheimer's disease 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, etc). Non-pharmacologic treatments include physical activity 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). Currently FDA-approved drugs for Alzheimer's disease include the cholinesterase inhibitors donepezil, rivastigmine, and galantamine, and the N-methyl-D-aspartate antagonist memantine. Cholinesterase inhibitors are indicated in mild, moderate, and severe Alzheimer's disease, while memantine is approved for moderate-to-severe disease. 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 associated with significant side effects. More recently, anti-amyloid monoclonal antibodies (e.g., lecanemab, donanemab) have been approved for early Alzheimer's disease and are intended to modify disease progression.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

In January 2023, the FDA granted accelerated approval to Leqembi for the treatment of Alzheimer's disease. The label notes that treatment should be initiated in patients with mild cognitive impairment or mild dementia stage of disease. This approval was converted to traditional approval in July 2023 based on data from the confirmatory Clarity AD trial.

Kisunla was approved in July 2024 for the treatment of Alzheimer's disease. Treatment should be initiated in patients with mild cognitive impairment or mild dementia stage of disease.

Policy # 00754

Original Effective Date: 09/13/2021

Current Effective Date: 09/01/2026

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

Leqembi

The efficacy of Leqembi was evaluated in two double-blind, placebo-controlled trials, in patients with Alzheimer's disease.

Study 1 (also known as Study 201) included patients with confirmed presence of amyloid pathology and mild cognitive impairment [64% of patients] or mild dementia stage of disease [36% of patients], consistent with Stage 3 and Stage 4 Alzheimer's disease. The study had a 79-week double-blind, placebo-controlled period, followed by 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.

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 ApoE ϵ 4 carriers. During the study, the protocol was amended to no longer randomize ApoE ϵ 4 carriers to the 10 mg/kg every two weeks dose arm. ApoE ϵ 4 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 ApoE ϵ 4 carriers. At baseline, the mean age of randomized patients was 71 years, with a range of 50 to 90 years. 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 MMSE score of ≥ 22 , 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). Patients were enrolled with or without concomitant approved therapies for Alzheimer's disease.

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 this substudy demonstrated a reduction in brain amyloid beta plaque with Leqembi 10 mg/kg every 2 weeks compared to placebo.

The primary endpoint of Study 1 was change from baseline on a weighted composite score consisting of selected items from the CDR-SB, MMSE, and 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%.

Study 2 (also known as the Clarity AD trial or Study 301) included 1795 participants and had a primary endpoint of change from baseline on the CDR-SB. In both trials, the difference in the rate of change between Leqembi (10 mg/kg biweekly) and placebo was approximately 27% favoring Leqembi for the primary endpoint at 18 months. This difference corresponds to a delay in the rate of cognitive decline for Leqembi vs placebo of approximately 5 months by the end of 18 months.

Policy # 00754

Original Effective Date: 09/13/2021

Current Effective Date: 09/01/2026

The observed difference (27%) was larger than the difference pre-specified in the power calculation of the study of 25%. In Study 2, the rate of decline for all 4 secondary cognitive and functional outcomes were statistically significantly slower in the Leqembi group. From a safety perspective, deaths were reported in 0.7% of the participants in the Leqembi group of Study 2 compared to 0.8% in the placebo group. Adverse events occurred more frequently in the Leqembi group and were driven by infusion-related reactions (any reaction, 26%; serious reaction, 1.2%) and ARIA with edema or effusions (ARIA-E; any ARIA-E, 13%, serious ARIA-E, 0.8%). The incidence of ARIA is higher in ApoE ϵ 4 homozygotes. Subgroup analyses suggested that the cognitive benefit of Leqembi may be smaller in ApoE ϵ 4 homozygotes. In the Study 2 open-label extension, there were 3 deaths for which a role for Leqembi could not be ruled out; 2 of the deaths were associated with a cerebral hemorrhage that occurred in ApoE ϵ 4 homozygous individuals with underlying severe cerebral amyloid angiopathy.

Longer-term data from the Clarity AD open-label extension demonstrate the durability of treatment effect with continued therapy. Across the core study and extension, treatment with Leqembi for up to 3 years resulted in approximately 0.95 points less decline on the CDR-SB compared with expected natural history progression, suggesting continued slowing of disease progression over time. Additional analyses extending to 4 years of treatment demonstrate further separation from expected decline (approximately 1.75 point difference on the CDR-SB versus external cohort data), with the magnitude of benefit increasing over time.

Leqembi Iqlik approval relied upon existing safety and efficacy information for Leqembi. It was evaluated in a sub-group analysis of the open-label extension of Study 2. In this analysis, it was found that transitioning to Leqembi Iqlik 360 mg SC once weekly after 18 months of the initiation dose maintains clinical and biomarker benefits comparable with continued IV dosing.

Kisunla

The efficacy of Kisunla was evaluated in a double-blind, placebo-controlled, parallel-group study in patients with Alzheimer's disease (patients with confirmed presence of amyloid pathology [confirmed by amyloid PET imaging with florbetapir or florbetaben] and mild cognitive impairment or mild dementia stage of disease, consistent with Stage 3 and Stage 4 Alzheimer's disease). Patients were enrolled with a Mini-Mental State Examination (MMSE) score of ≥ 20 and ≤ 28 and had a progressive change in memory function for at least 6 months. Patients in the study were stratified based on visual assessment of tau PET imaging with flortaucipir and standardized uptake value ratio (SUVR). Patients were enrolled with or without concomitant approved therapies (cholinesterase inhibitors and the N-methyl-D-aspartate antagonist memantine) for Alzheimer's disease.

In the study, 1736 patients were randomized 1:1 to receive 700 mg of Kisunla every 4 weeks for the first 3 doses, and then 1400 mg every 4 weeks ($n = 860$) or placebo ($n = 876$) for a total of up to 72 weeks. The treatment was switched to placebo based on amyloid PET levels measured at Week 24, Week 52, and Week 76. If the amyloid plaque level was < 11 Centiloids on a single PET scan or 11 to < 25 Centiloids on 2 consecutive PET scans, the patient was eligible to be switched to placebo. Dose adjustments were allowed for treatment-emergent ARIA or symptoms that then showed ARIA-E or ARIA-H on MRI.

Policy # 00754

Original Effective Date: 09/13/2021

Current Effective Date: 09/01/2026

At baseline, mean age was 73 years, with a range of 59 to 86 years. Of the total number of patients randomized, 68% had low/medium tau level and 32% had high tau level; 71% were ApoE ε4 carriers and 29% were ApoE ε4 non-carriers.

The primary efficacy endpoint was change in the integrated Alzheimer's Disease Rating Scale (iADRS) score from baseline to 76 weeks. The iADRS is a combination of two scores: the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog₁₃) and the Alzheimer's Disease Cooperative Study- instrumental Activities of Daily Living (ADCS-iADL) scale. The total score ranges from 0 to 144 with lower scores reflecting worse cognitive and functional performance. Other efficacy endpoints included Clinical Dementia Rating Scale- Sum of Boxes, ADAS-Cog₁₃, and ADCS-iADL.

There were two primary analysis populations based on tau PET imaging with flortaucipir: 1) low/medium tau level population (defined by visual assessment and SUVR of ≥ 1.10 and ≤ 1.46) and 2) combined population of low/medium plus high tau (defined by visual assessment and SUVR > 1.46) population.

Patients treated with Kisunla demonstrated a statistically significant reduction in clinical decline on iADRS compared to placebo at Week 76 in the combined population (2.92, $p < 0.0001$) and the low/medium tau population (3.25, $p < 0.0001$).

Patients treated with Kisunla demonstrated a statistically significant reduction in clinical decline on CDR-SB compared to placebo at Week 76 in the combined population (-0.70, $p < 0.0001$). There were also statistically significant differences between treatment groups as measured by ADAS-Cog₁₃ and ADCS-iADL at Week 76.

Dosing was continued or stopped in response to observed effects on amyloid imaging. The percentages of patients eligible for switch to placebo based on amyloid PET levels at Week 24, Week 52, and Week 76 timepoints were 17%, 47%, and 69% respectively.

References

1. Leqembi, Lecanemab Autoinjector [package insert]. Eisai Inc. Nutley, New Jersey. Updated August 2025.
2. 2021 Alzheimer's disease facts and figures. Alzheimer's Dement. Mar 2021; 17(3): 327-406.
3. Alzheimer's Association. 2021 Alzheimer's disease facts and figures. Published 2021. Available at <https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf>.
4. Roberts RO, Aakre JA, Kremers WK, et al. Prevalence and Outcomes of Amyloid Positivity Among Persons Without Dementia in a Longitudinal, Population-Based Setting. JAMA Neurol. Aug 01 2018; 75(8): 970-979.
5. Elias-Sonnenschein LS, Viechtbauer W, Ramakers IH, et al. Predictive value of APOE-4 allele for progression from MCI to AD-type dementia: a meta-analysis. J Neurol Neurosurg Psychiatry. Oct 2011; 82(10): 1149-56.
6. Mattsson N, Groot C, Jansen WJ, et al. Prevalence of the apolipoprotein E 4 allele in amyloid positive subjects across the spectrum of Alzheimer's disease. Alzheimer's Dement. Jul 2018; 14(7): 913-924.

Policy # 00754

Original Effective Date: 09/13/2021

Current Effective Date: 09/01/2026

7. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA. Oct 1997; 278(16): 1349-56.
8. Bekris LM, Yu CE, Bird TD, et al. Genetics of Alzheimer disease. J Geriatr Psychiatry Neurol. Dec 2010; 23(4): 213-27.
9. Vermunt L, Sikkes SAM, van den Hout A, et al. Duration of preclinical, prodromal, and dementia stages of Alzheimer's disease in relation to age, sex, and APOE genotype. Alzheimer's Dement. Jul 2019; 15(7): 888-898.
10. Combined FDA and Applicant PCNS Drugs Advisory Committee Briefing Document: Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee Meeting- November 6, 2020. Available at <https://www.fda.gov/media/143502/download>
11. Reuben DB, Tan ZS, Romero T, et al. Patient and Caregiver Benefit From a Comprehensive Dementia Care Program: 1-Year Results From the UCLA Alzheimer's and Dementia Care Program. J Am Geriatr Soc. Nov 2019; 67(11): 2267-2273.
12. Gronek P, Balko S, Gronek J, et al. Physical Activity and Alzheimer's Disease: A Narrative Review. Aging Dis. Dec 2019; 10(6): 1282-1292.
13. Du Z, Li Y, Li J, et al. Physical activity can improve cognition in patients with Alzheimer's disease: a systematic review and meta-analysis of randomized controlled trials. Clin Interv Aging. 2018; 13: 1593-1603.
14. Gitlin LN, Kales HC, Lyketsos CG. Nonpharmacologic management of behavioral symptoms in dementia. JAMA. Nov 21 2012; 308(19): 2020-9.
15. Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt HP, et al. Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials. BMJ. Aug 06 2005; 331(7512): 321-7.
16. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer's Dement. Apr 2018; 14(4): 535-562.
17. US Food and Drug Administration. Early Alzheimer's disease: developing drugs for treatment guidance for industry. Draft Guidance. Published online Feb 29, 2018. Available at <https://www.fda.gov/media/110903/download>.
18. US Food and Drug Administration. Draft guidance for industry on Alzheimer's disease: developing drugs for the treatment of early stage disease. Published online March 28, 2013. Available at https://isctm.org/public_access/FDAGuidance_AD_Developing_Drugs_Early_Stage_Treatment.pdf.
19. Liu KY, Schneider LS, Howard R. The need to show minimum clinically important differences in Alzheimer's disease trials. Lancet Psychiatry. Jun 01 2021.
20. Cedarbaum JM, Jaros M, Hernandez C, et al. Rationale for use of the Clinical Dementia Rating Sum of Boxes as a primary outcome measure for Alzheimer's disease clinical trials. Alzheimer's Dement. Feb 2013; 9(1 Suppl): S45-55.
21. Andrews JS, Desai U, Kirson NY, et al. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. Alzheimer's Dement (N Y). 2019; 5: 354-363.
22. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. Nov 1975; 12(3): 189-98.

Policy # 00754

Original Effective Date: 09/13/2021

Current Effective Date: 09/01/2026

23. Chapman KR, Bing-Canar H, Alosco ML, et al. Mini Mental State Examination and Logical Memory scores for entry into Alzheimer's disease trials. *Alzheimer's Res Ther.* Feb 22 2016; 8: 9.
24. Franco-Marina F, Garcia-Gonzalez JJ, Wagner-Echeagaray F, et al. The Mini-mental State Examination revisited: ceiling and floor effects after score adjustment for educational level in an aging Mexican population. *Int Psychogeriatr.* Feb 2010; 22(1): 72-81.
25. Galasko D, Abramson I, Corey-Bloom J, et al. Repeated exposure to the Mini-Mental State Examination and the Information-Memory-Concentration Test results in a practice effect in Alzheimer's disease. *Neurology.* Aug 1993; 43(8): 1559-63.
26. Spencer RJ, Wendell CR, Giggey PP, et al. Psychometric limitations of the mini-mental state examination among nondemented older adults: an evaluation of neurocognitive and magnetic resonance imaging correlates. *Exp Aging Res.* 2013; 39(4): 382-97.
27. Mohs RC, Knopman D, Petersen RC, et al. Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's Disease Assessment Scale that broaden its scope. *The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord.* 1997; 11 Suppl 2: S13-21.
28. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry.* Nov 1984; 141(11): 1356-64.
29. Schrag A, Schott JM. What is the clinically relevant change on the ADAS-Cog?. *J Neurol Neurosurg Psychiatry.* Feb 2012; 83(2): 171-3.
30. McDougall F, Edgar C, Mertes M, et al. Psychometric Properties of the Clinical Dementia Rating - Sum of Boxes and Other Cognitive and Functional Outcomes in a Prodromal Alzheimer's Disease Population. *J Prev Alzheimers Dis.* 2021; 8(2): 151-160.
31. Vellas B, Bateman R, Blennow K, et al. Endpoints for Pre-Dementia AD Trials: A Report from the EU/US/CTAD Task Force. *J Prev Alzheimers Dis.* Jun 2015; 2(2): 128-135.
32. Bullock R, Touchon J, Bergman H, et al. Rivastigmine and donepezil treatment in moderate to moderately-severe Alzheimer's disease over a 2-year period. *Curr Med Res Opin.* Aug 2005; 21(8): 1317-27.
33. Tariot PN, Solomon PR, Morris JC, et al. A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. *Neurology.* Jun 27 2000; 54(12): 2269-76.
34. Doody RS, Thomas RG, Farlow M, et al. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. *N Engl J Med.* Jan 23 2014; 370(4): 311-21.
35. Cummings J. The Neuropsychiatric Inventory: Development and Applications. *J Geriatr Psychiatry Neurol.* Mar 2020; 33(2): 73-84.
36. Howard R, Phillips P, Johnson T, et al. Determining the minimum clinically important differences for outcomes in the DOMINO trial. *Int J Geriatr Psychiatry.* Aug 2011; 26(8): 812-7.
37. Sevigny J, Chiao P, Bussiere T, et al. The antibody aducanumab reduces A plaques in Alzheimer's disease. *Nature.* Sep 01 2016; 537(7618): 50-6.
38. FDA Pre-Recorded Presentation Slides for the November 6, 2020: Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee. Available at <https://www.fda.gov/media/143504/download>.
39. Beta-Amyloid Antibodies for Early Alzheimer's Disease. Draft Evidence Report. Institute for Clinical and Economic Review (ICER). Updated December 2022.

Monoclonal Antibodies for the Treatment of Alzheimer's Disease

Policy # 00754

Original Effective Date: 09/13/2021

Current Effective Date: 09/01/2026

40. Lecanemab for Early Alzheimer's Disease Final Evidence Report. Institute for Clinical and Economic Review (ICER). Updated April 2023.
41. Hoiland-Carlsen PF, Alavi A, Barrio JR, et al. Donanemab, another anti-Alzheimer's drug with Risk and Uncertain Benefit. *Ageing Research Reviews*. August 2024; 99:1568-1637.
42. Kisunla [package insert]. Eli Lilly and Company. Indianapolis, IN. Updated July 2024.
43. Leqembi IQLIK Drug Evaluation. Express Scripts. Updated September 2025.
44. Nonino F, et al. Anti-amyloid monoclonal antibodies for Alzheimer's disease. *Cochrane Database Syst Rev*. 2026;CD016297.
45. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*. 1993;43(11):2412-2414
46. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State." A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198.
47. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695-699.

Policy History

Original Effective Date: 09/13/2021

Current Effective Date: 09/01/2026

- | | |
|------------|--|
| 08/05/2021 | Medical Policy Committee review |
| 08/11/2021 | Medical Policy Implementation Committee approval. New policy. |
| 12/20/2021 | Coding update |
| 08/04/2022 | Medical Policy Committee review |
| 08/10/2022 | Medical Policy Implementation Committee approval. No change to coverage. |
| 06/01/2023 | Medical Policy Committee review |
| 06/14/2023 | Medical Policy Implementation Committee approval. Added new drug, Leqembi, to policy. Changed title to "Monoclonal Antibodies for the Treatment of Alzheimer's Disease" |
| 08/10/2023 | Coding update |
| 08/01/2024 | Medical Policy Committee review |
| 08/14/2024 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Background, Rationale and Reference information updated in sections. |
| 11/07/2024 | Medical Policy Committee review |
| 11/13/2024 | Medical Policy Implementation Committee approval. Updated policy to remove obsolete drug, Aduhelm, and add new drug, Kisunla. |
| 12/04/2025 | Medical Policy Committee review |
| 12/10/2025 | Medical Policy Implementation Committee approval. Added new product, Leqembi IQLIK to policy with relevant criteria and background information. |
| 07/21/2026 | Pre-Pharmacy and Therapeutics Committee approval. |
| 07/22/2026 | Pharmacy and Therapeutics Committee approval. Added coverage criteria for Leqembi and Kisunla and updated relevant background information. Created new Policy Guidelines Section reflecting appropriate dosing and monitoring requirements for these products. |

Next Scheduled Review Date: 07/2027

Policy # 00754

Original Effective Date: 09/13/2021

Current Effective Date: 09/01/2026

Coding

The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2025 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Louisiana Blue Medical Policy Coverage Guidelines is with Louisiana Blue and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Louisiana Blue Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Louisiana Blue Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	C9399, J3490, J3590, J0174, J0175
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

Monoclonal Antibodies for the Treatment of Alzheimer's Disease

Policy # 00754

Original Effective Date: 09/13/2021

Current Effective Date: 09/01/2026

****Medically Necessary (or "Medical Necessity")** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

NOTICE: If an authorization for an ongoing course of treatment has been provided to a member and the member changes from one health plan to another health plan (e.g., a member moves from carrier A to Louisiana Blue), Louisiana Blue may honor the previous health plan's authorization for the same service under the same type of in-network benefit for a 90-day transition period. Documentation of the authorization for the ongoing course of treatment from the previous health plan must be provided to us by the member or their provider and the services provided for the course of treatment must otherwise be a covered service under the Louisiana Blue health plan. This provision does not apply to medications covered under the plan's pharmacy benefit.