LOUISIANA BLUE

Monoclonal Antibodies for the Treatment of Alzheimer's Disease

Policy # 00754
Original Effective Date: 09/13/2021
Current Effective Date: 11/25/2024

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.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of lecanemab-irmb (Leqembi™)‡ or donanemab-azbt (Kisunla™)‡ in patients with Alzheimer's disease in the mild cognitive impairment or mild dementia stage of disease 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) or donanemab-azbt (Kisunla) for non-FDA approved indications to be **investigational.***

Background/Overview

Leqembi and Kisunla are monoclonal antibodies directed against soluble and insoluble forms of beta-amyloid, a proposed cause 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 dosed at 10 mg/kg intravenously every two weeks. Kisunla is dosed as 700 mg intravenously every 4 weeks for 3 doses, then 1400 mg every 4 weeks. Additionally, the product labels recommend that a baseline brain magnetic resonance imaging (MRI) must be done within 1 year prior to initiating treatment due to the risk of amyloid-related imaging abnormalities (ARIA). Subsequently, MRI should be repeated prior to the 5th, 7th, and 14th infusions of Leqembi and the 2nd, 3rd, 4th, and 7th infusions of Kisunla. If radiographic severe ARIA-hemorrhage (ARIA-H) is observed, treatment may be continued with caution only after a clinical evaluation and a follow-up MRI demonstrates radiographic stabilization (i.e, no increase in size or number of ARIA-H). Additional recommendations are provided in the package inserts for the management of patients with ARIA-edema (ARIA-E) 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."

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. It is estimated that 6.2 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 and 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 ε4 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 ε4 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 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 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.

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.

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.

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 federal 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 ε4 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 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 ε4 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 $\geq$ 22, had objective impairment in episodic memory as indicated by at least 1 standard deviation below age-adjusted mean in the Wechsler-Meory 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. 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 ε4 homozygotes. Subgroup analyses suggested that the cognitive benefit of Leqembi may be smaller in ApoE ε4 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 ε4 homozygous individuals with underlying severe cerebral amyloid angiopathy.

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 $\geq$ 20 and $\leq$ 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.

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-Cog_{13}) 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 $\geq$ 1.10 and $\leq$ 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. Amyloid PET values may increase after treatment with Kisunla is stopped. There is no data beyond the 76-week duration of the study to guide whether additional dosing with Kisunla may be needed for longer-term clinical benefit.

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Policy History

Original Effective Date: 09/13/2021
Current Effective Date: 11/25/2024

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.

Next Scheduled Review Date: 11/2025

Policy # 00754
Original Effective Date: 09/13/2021
Current Effective Date: 11/25/2024

Coding

The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2023 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.

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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 Delete code effective 11/25/2024: J0172
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.

**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.

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.