MASSACHUSETTS

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Medical Policy

Monoclonal Antibodies for Treatment of Alzheimer's Disease

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Policy Number: 946

BCBSA Reference Number: 5.01.38
NCD/LCD: N/A

Related Policies

Lecanemab (Leqembi®) and Donanemab (Kisunla™) for Alzheimer's Disease Prior Authorization Request Form #949

Note:
Physicians are required to attest that the following requirements are met:

1. Physicians administering Lecanemab (Leqembi®) and Donanemab (Kisunla™) are required to be a participant in the CMS Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease CED Study Registry; and

(**Note**: While this registry does not collect data from Blue Cross Commercial members, providers are required to attest to being a participating provider in this CMS registry for their Medicare patients as a condition of rendering services to Blue Cross Commercial members.)

2. The Physician administering the drug practices in an appropriate setting with a structured data collection system that evaluates patient safety and harms, treatment benefits and efficacy, and overall improvement in patient health outcomes.

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

Lecanemab (Leqembi®) and Donanemab (Kisunla™) Initiation of Therapy (Approval Length 12 Months)

The use of lecanemab and donanemab may be considered **MEDICALLY NECESSARY** for the treatment of Alzheimer's Disease (AD), pending the availability of further data on risks and benefits, when **ALL** the following criteria and policy guidelines are met.

1. Meets criteria for mild cognitive impairment (MCI) or mild dementia stage of AD (see policy guidelines); **AND**
2. Presence of amyloid beta pathology* (see policy guidelines); **AND**

3. Access to an appropriate healthcare delivery model (see policy guidelines); **AND**
4. MRI* scan completed within previous 12 months which does **not** show:
    a. Evidence of a non-AD dementia; **OR**
    b. Evidence of significant pathological findings on brain MRI (see policy guidelines); **AND**
5. Does **not** have:
    a. Concurrent neurological condition(s), other than MCI or AD, contributing to cognitive impairment; **OR**
    b. History of stroke, transient ischemic attacks or seizures within 12 months prior to initiating treatment with lecanemab; **OR**
    c. Bleeding disorder that is inadequately controlled (including a platelet count <50,000 or international normalized ratio [INR] >1.5); **AND**
6. If receiving anticoagulant therapy, anticoagulant status should be optimized, and individual should be on a stable dose for 4 weeks prior to initiating treatment with lecanemab; **AND**
7. Not receiving another anti-amyloid monoclonal antibody; **AND**
8. Is prescribed in accordance with the U.S. Food and Drug Administration (FDA) approved prescribing label** (see policy guidelines).

Note:
*PET scans and MRIs require prior authorization from Carelon High Technology Radiology Management Program. For medical necessity criteria, see Carelon Medical Benefits Management Clinical Guidelines for Advanced Imaging/Radiology.

** ApoE genotype testing requires prior authorization from Carelon Genetic Testing Management Program. For medical necessity criteria, see Carelon Medical Benefits Management Clinical Guidelines.

Policy Guidelines Initiation of Therapy

Diagnosis of Mild Cognitive Impairment or Mild Dementia
Lecanemab was evaluated in the pivotal trial called Clarity AD (Clinical Trial NCT03887455).
Donanemab was evaluated in the pivotal trial called Trailblazer-ALZ 2 for AD (Clinical Trial NCT04437511).

Mild cognitive impairment (MCI) due to Alzheimer disease (AD)–intermediate likelihood:
1. Meet the National Institute of Aging–Alzheimer's Association (NIA-AA) core clinical criteria for MCI due to AD–intermediate likelihood.
2. Documentation that the patient is independent of all basic activities with daily living.
3. Report a history of subjective memory decline with gradual onset and slow progression over the last 1 year which is corroborated by an informant.

Mild AD dementia:
1. Meet the NIA-AA core clinical criteria for probable AD dementia.
2. Documentation that the patient is independent of all basic activities with daily living.

Positive Amyloid Pathology
At least 1 of the following:
1. Positron emission tomography (PET) assessment of imaging agent uptake into brain within 12 months.
2. Cerebrospinal fluid (CSF) assessment of t-tau/Aβ[1-42] or p-tau/Aβ[1-42].

Healthcare Delivery Model
An appropriate healthcare delivery model for lecanemab would include care delivered in a setting that may include access to:
1. Trained and experienced psychometricians, neuropsychiatrists, neurologists, geriatric psychiatrists and/or geriatricians to diagnose and stage Alzheimer disease.
2. Trained and experienced radiologists to interpret amyloid PET scans.

3. Trained and experienced radiologists for MRI interpretation for superficial siderosis and micro hemorrhages.
4. Protocol for the management of serious and severe ARIA.
5. Individual receiving lecanemab preferably has an informant/care partner as part of discussion for treatment initiation, continuation, and monitoring.

Exclusionary Pathological Findings on MRI
Excluded patients with significant pathological findings on brain MRI, including but not limited to:

1. More than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter).
2. A single macrohemorrhage greater than 10 mm at greatest diameter.
3. An area of superficial siderosis.
4. Evidence of vasogenic edema.
5. Evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions.
6. Evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease.
7. Space occupying lesions.
8. Brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary.

FDA Label Recommended Dose
Lecanemab: Per the label, the recommended dosage is 10 mg/kg that must be diluted then administered as an intravenous infusion over approximately one hour, once every two weeks.
Donanemab: Per label, the recommended dosage is 700 mg administered as an intravenous infusion every four weeks for the first three doses, followed by 1400 mg every four weeks.

Per the label, Donanemab is administered every four weeks as an intravenous infusion over approximately 30 minutes. Consider stopping dosing with donanemab based on reduction of amyloid plaques to minimal levels on amyloid PET imaging.

Monitoring
The product label of lecanemab recommends that a baseline brain MRI within 1 year must be done prior to initiating treatment due to the risk of ARIA. Subsequently, MRI should be repeated prior to the fifth, seventh, and fourteenth infusions. Follow recommendations for dosing interruptions in patients with ARIA as specified in the US FDA approved prescribing label.

The product label of donanemab recommends obtaining an MRI prior to the second, third, fourth, and seventh infusions.

Boxed Warning
The product label includes a boxed warning regarding the risk of ARIA. The warning states that providers should discuss the potential risk of serious adverse events associated with ARIA when deciding to initiate treatment. The warning also states that patients who are ApoE ε4 homozygotes have a higher incidence of ARIA and testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA.

Lecanemab (Leqembi®) and Donanemab (Kisunla™) Continuation of Therapy (Approval Length 12 Months)

After the initial 12-month approval and the initial treatment is near the end of the 12 months, incremental reauthorization of lecanemab and Donanemab may be considered **MEDICALLY NECESSARY** for the treatment of Alzheimer disease (AD), pending accumulation of further data on risks and benefits, when **ALL** the following criteria and policy guidelines are met:

1. AD has not progressed to severe dementia; **AND**

2. Has received MRI during treatment with lecanemab according to schedule recommended in FDA label to monitor for amyloid-related imaging abnormalities (ARIA - see policy guidelines) which does **not** show:
    a. ARIA of the severity that meets recommendations for dosing interruptions provided in the FDA label (see policy guidelines), **OR**
    b. Development of an additional brain disease likely to account for greater cognitive symptoms than Alzheimer disease.

Policy Guidelines Continuation of Therapy

ARIA
The product label recommends that a baseline brain magnetic resonance imaging (MRI) within 1 year must be done prior to initiating treatment due to the risk of developing amyloid-related imaging abnormalities (ARIA). Subsequently, MRI should be repeated prior to the 5th, 7th and 14th infusions. If radiographically 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).

Exclusionary pathological findings on MRI
Excluded patients with significant pathological findings on brain MRI, including but not limited to:

1. More than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter).
2. A single macrohemorrhage greater than 10 mm at greatest diameter.
3. An area of superficial siderosis.
4. Evidence of vasogenic edema.
5. Evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions.
6. Evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease.
7. Space occupying lesions
8. Brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary.

Lecanemab and Donanemab are considered **INVESTIGATIONAL** for all other indications and when the above criteria and policy guidelines are not met.

Prior Authorization Information

Inpatient
- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient
- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is **required for Lecanemab and Donanemab**
Commercial PPO and Indemnity	Prior authorization is **required for Lecanemab and Donanemab**

Requesting Prior Authorization Using Authorization Manager
Providers will need to use Authorization Manager to submit initial authorization requests for services. Authorization Manager, available 24/7, is the quickest way to review authorization requirements, request authorizations, submit clinical documentation, check existing case status, and view/print the decision letter. For commercial members, the requests must meet medical policy guidelines.

To ensure the request is processed accurately and quickly:
- Enter the facility's NPI or provider ID for where services are being performed.
- Enter the appropriate surgeon's NPI or provider ID as the servicing provider, *not* the billing group.

Authorization Manager Resources
- Refer to our Authorization Manager page for tips, guides, and video demonstrations.

Complete Prior Authorization Request Form for **Lecanemab (Leqembi®) and Donanemab (Kisunla™) for Alzheimer's Disease** (949) using Authorization Manager.

For out of network providers: Requests should still be faxed to 888-973-0726.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following code to be covered for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:

HCPCS Codes

HCPCS codes:	Code Description
J0174	Injection, lecanemab-irmb, 1 mg (eff 7/6/2023)
J0175	Injection, donanemab-azbt, 2 mg

Background

Alzheimer Disease

Alzheimer 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 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 disease dementia, and the number is projected to reach over 12 million by 2050.[1]

Pathophysiology

The pathologic hallmarks of AD are extracellular deposits of amyloid beta, 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 AD is not well understood. Generally referred to as the "amyloid hypothesis", it is believed that aggregation of amyloid beta oligomers in the brain leads to amyloid plaques, and it is 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.[2,3]

Salient known risk factors for AD are older age, genetics, and family history. Of these, increasing age has the largest known impact on risk of developing AD. While several genes have been found to increase the risk of AD, the ε4 allele of the apolipoprotein E (*ApoE*) gene is the strongest known genetic risk

factor.[4,5] Having a single copy of the gene is associated with a 2- to 3-fold increase in developing AD while 2 copies of the gene may increase risk of AD by as much as 15 times.[6] Approximately two-thirds of pathology-confirmed AD cases are ε4 positive (homozygous or heterozygous), compared with about 15% to 20% of the general population.[5] Autosomal dominant genetic mutations are estimated to account for less than 1% of AD cases.[7]

The pathophysiological changes and clinical manifestations of AD are progressive and occur along a continuum, and accumulation of amyloid beta may begin 20 years or more before symptoms arise.[8] The 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 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. 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.

Clinical criteria for diagnosing AD are informed by the NIA-AA 2011 guidelines.[10,11] Mild cognitive impairment (MCI) lies between the cognitive changes of normal aging and dementia. Mild cognitive impairment is a syndrome in which persons experience memory loss (amnestic MCI) or loss of thinking skills other than memory loss (non-amnestic MCI), to a greater extent than expected for age, but without impairment of day-to-day functioning.[10] Individuals with MCI are at increased risk of developing dementia (whether from AD or another etiology), but many do not progress to dementia, and some get better. Dementia is a syndrome involving cognitive and behavioral impairment in an otherwise alert patient, due to a number of neurological diseases, alone or combined. It is not a specific cause or disease process itself. The impairment must involve a minimum of 2 domains (memory, reasoning, visuospatial abilities, language or personality behaviors), impact daily functioning, represent a decline from previous levels of functioning, not be explainable by delirium (a temporary state of mental confusion and fluctuating consciousness from various causes) or a major psychiatric disorder, and be objectively documented by a "bedside" mental status exam (e.g., the mini-mental status exam) or neuropsychological testing.[11] These guidelines describe core clinical criteria for "all-cause" dementia and "probable AD" dementia. Briefly, "probable AD" dementia must first meet the criteria for "all-cause" dementia. Additionally, there must be: (a) insidious onset; (b) documented worsening of cognition; (c) exclusion of major concomitant cerebrovascular disease (as most individuals with AD have some level of this as well); and (d) exclusion of alternative diagnoses (e.g., dementia with Lewy bodies, behavioral variant frontotemporal dementia, progressive aphasia, or other neurological disease associated with dementia). A clinical diagnosis of "possible AD" dementia would meet the criteria for "probable AD" with the exception of having an "atypical course" (e.g., sudden rather than insidious onset) or an "etiologically mixed presentation."

Many tests are available in the market to detect the underlying core pathology such as certain biomarkers in the cerebrospinal fluid (CSF) (eg, decreased amyloid beta and increased CSF tau protein levels) and 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 CSF tests for amyloid beta confirmation that are currently in development in the US. Cerebrospinal fluid tests and amyloid PET tracers are routinely used in the enrollment of participants in contemporary AD studies.[12]

Current Treatment

Treatment goals for patients with AD are often directed to maintain quality of life, treat cognitive symptoms, and manage behavioral and psychological symptoms of dementia. Treatment remains largely supportive, including creation and implementation of individualized dementia care plans, caregiver education and support, care navigation, care coordination, and referral to community-based organizations for services (eg, adult day care, caregiver training).[13] Non-pharmacologic treatments include physical activity[14,15] as well as behavioral strategies to ameliorate neuropsychiatric symptoms (eg, agitation, delusions, disinhibition), and problem behaviors (eg, resistance to care, hoarding, obsessive-compulsive behaviors).[16] Currently, FDA-approved drugs for AD include cholinesterase inhibitors, donepezil,

rivastigmine, and galantamine, and the N-methyl-D-aspartate antagonist, memantine. Cholinesterase inhibitors are indicated in mild, moderate, and severe AD, while memantine is approved for moderate-to-severe AD. These drugs, either alone or in combination, focus on managing cognitive and functional symptoms of the disease and have not been shown to alter disease trajectory. The evidence for efficacy is limited and these agents are associated with significant side effects.[16,17,]

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

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)[16]

[a]Applicable only to individuals in the Alzheimer continuum that fall into 1 of the 4 biomarker groups:

1. A+T+N+
2. A+T-N-
3. A+T+N-
4. A+T-N+ where A: Aggregated Aβ or associated pathologic state (CSF Aβ42, or Aβ42/Aβ40 ratio or Amyloid PET), T: Aggregated tau (neurofibrillary tangles) or associated pathologic state (CSF phosphorylated tau or Tau PET) and N: Neurodegeneration or neuronal injury (anatomic MRI, FDG PET or CSF total tau)

For stages 1 to 6: Cognitive test performance may be compared to normative data of the investigators choice, with or without adjustment (choice of the investigators) for age, sex, education, etc.
For stages 2 to 6: Although cognition is the core feature, neurobehavioral changes—for example, changes in mood, anxiety, or motivation—may coexist.
For stages 3 to 6: Cognitive impairment may be characterized by presentations that are not primarily amnestic.

CSF: cerebrospinal fluid; FDG: fluorodeoxyglucose; MCI: mild cognitive impairment; MRI: magnetic resonance imaging; PET: positron emission tomography.

Summary of Evidence

Lecanemab

For individuals with early AD (MCI or mild dementia due to AD) who receive lecanemab, the evidence includes 2 double-blind RCTs with samples sizes of 390 and 1795. Both trials reported an approximately 27% statistically significantly slower rate of decline for the primary cognitive and functional outcome (ADCOMS for Study 201; CDR-SB for Study 301) for lecanemab versus placebo. In the phase 3 Study 301 (Clarity AD), the rate of decline for all 4 secondary cognitive and functional outcomes were statistically significant favoring lecanemab. Measures of quality of life and caregiver burden also favored lecanemab. ARIA was observed in 21% (191/898) of patients treated with lecanemab compared to 9% (84/897) on placebo. Symptomatic ARIA occurred in 3% (29/898) of patients treated with lecanemab. The incidence of ARIA was higher in ApoE ε4 homozygotes.

The clinical development program of lecanemab includes 3 studies that are summarized in Table 9.

Trial	Phase	Description	N	Design	Status
Study 201 (Study 1 in the prescribing label)	2	Dose regimen-finding trial in early AD (i.e., MCI due to AD and mild AD dementia).	856	DB RCT	Core: 18 months (completed and published) OLE: Up to 5 years[48,49,]
Clarity AD (Study 301, study 2 in the prescribing label)	3	Phase 3 confirmatory study in early AD (i.e., MCI due to AD and mild AD dementia).	1795	DB RCT	Core: 18 months (completed and published)[50,] OLE: up to 2 years (ongoing)
AHEAD 3-45 Study	3	Phase 3 study to assess if lecanemab can slow accumulation of amyloid, tau, and prevent cognitive decline in cognitively unimpaired individuals (i.e., preclinical AD): intermediate amyloid (20 to 40 centiloids) and elevated amyloid (>40 centiloids)	1400	DB RCT	Ongoing

Lecanemab was approved by the FDA on January 6, 2023, under the accelerated approval pathway based on reduction in amyloid plaque. The accelerated approval was converted to a traditional approval in July 2023 based on results of the Clarity trial.

Table 9. Trial characteristics are summarized below:

Leqembi Trial Characteristics	
Study 201 (Study 1 in the prescribing label [51,52]	
Country	Multinational (US, Canada, EU, UK, Asia)
Design	RCT
Sites	169
Duration	78-months (79-week double-blind, placebo-controlled period, followed by an open-label extension period for up to 260 weeks)
Intervention	• Participants randomized[c] to lecanemab

	• 2.5 mg biweekly (n=52) • 5 mg biweekly (n=89) • 10 mg biweekly (n=152) • 5 mg monthly (n=48) • 10 mg monthly (n=246)
Comparator	Placebo

Participants	• 50 to 90 years of age
	• Confirmed presence of amyloid pathology
	• MCI or mild dementia as defined by by the 2011 NIA-AA framework[a] with evidence of brain Aβ pathology by either visual read of a PET scan or CSF assessment of Aβ1-42. Participants were also required to have:
	  ○ CDR global score of 0.5 or 1.0
	  ○ Memory Box score of 0.5 or greater
	  ○ MMSE score of ≥22
	  ○ Objective impairment in episodic memory as indicated by at least 1 standard deviation below age-adjusted mean in the WMS-IV LMII subscale.
	• Primary clinical endpoint: Change from baseline in ADCOMS at week 53.[b]
	• Secondary endpoints: brain amyloid plaque content, pharmacokinetics, and immunogenicity
	• Clinical efficacy endpoints were exploratory.

Clarity AD. Study 301 (Study 2 in the prescribing label [51,53,50])	
Country	Multinational (US, Australia, Canada, China, France, Germany, Italy, Japan, Korea, Russia, Singapore, Spain, Sweden, United Kingdom
Design	RCT
Sites	235
Duration	78-week placebo-controlled period, with safety follow-up period of 3 months
Intervention	Lecanemab 10 mg/kg biweekly, n=898
Comparator	Placebo n=897
Participants	• 50 to 90 years of age • AD with confirmed presence of amyloid pathology and mild cognitive impairment (62%) or mild dementia stage of disease (38%) • Clinical Dementia Rating (CDR) global score of 0.5 or 1.0 and a Memory Box score of 0.5 or greater • MMSE score of ≥22 and ≤30 • Objective impairment in episodic memory • 69% ApoE ε4 carriers; 31% were ApoE ε4 non-carriers • Median age 72 years (range of 50 to 90) • 52% women • 1381 (77%) White; 303 (17%) Asian; 47 (3%) were Black

ApoE ε4: *apolipoprotein E ε4*; ADCOMS: Alzheimer's Disease Composite Score; CDR: Clinical Dementia Rating; CSF: cerebrospinal fluid; MCI: mild cognitive impairment; MMSE: Mini-Mental State Examination; NIA-AA: National Institute on Aging-Alzheimer's Association; PET: positron emission tomography; RCT: randomized controlled trial; WMS-IV LMII: Wechsler-Memory Scale-IV Logical Memory II

[a] Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease[10,11]

[b] Change from baseline in brain amyloid plaque as measured by 18F-florbetapir PET and quantified by a composite standard uptake value ratio (SUVR) was assessed in a subset of patients at week 53 and week 79 and serves as the endpoint to support accelerated approval.

[c] Randomization stratified by clinical subgroups (MCI due to Alzheimer's disease and mild Alzheimer's disease dementia), ApoE ε4 carrier status (carrier or non-carrier), and ongoing treatment with concurrent medications for treatment of Alzheimer's disease

Study 201 was a dose-finding double-blind, placebo-controlled trial. Lecanemab 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%. Change from baseline in brain amyloid plaque as measured by 18F-florbetapir PET and quantified by a composite SUVR was assessed in a subset of patients at week 79 and serves as the endpoint to support accelerated approval. Treatment with lecanemab 10 mg/kg every 2 weeks reduced amyloid beta plaque levels in the brain, producing reductions in PET SUVR compared to placebo at both weeks 53 and 79 (p<.001). The magnitude of the reduction was time- and dose-dependent. During an off-treatment period (range from 9 to 59 months; mean of 24 months), SUVR and centiloid values began to increase with a mean rate of increase of 2.6 centiloids/year. However, treatment difference relative to placebo at the end of the double-blind, placebo-controlled period was maintained [51,52].

Study 301 (Claridy AD, study 2 in the prescribing label) was a multicenter, randomized, double-blind, placebo-controlled trial comparing 10 mg/kg biweekly lecanemab (n=898) to placebo (n=897). The primary efficacy endpoint was the change from baseline in CDR-SB at 18 months. The rate of decline in CDR-SB was statistically significantly slower in the lecanemab group. Change from baseline at 18 months in amyloid burden on PET as measured in centiloids in the subgroup tested and change from baseline at 18 months in the ADAS-cog14 score, change from baseline at 18 months in the ADCOMS, and change from baseline at 18 months in the ADCS-MCI-ADL score, were all statistically significant favoring lecanemab. Subgroup analyses for the primary and secondary cognitive outcomes were performed for demographic and baseline characteristics, including APOE. Treatment comparisons favored lecanemab in all subgroups across the outcome measures tested except for the CDR-SB outcome in APOE ε4 homozygous participants which favored placebo (n=132 vs 136 in placebo vs lecanemab). While results for ADAS-Cog 14 and ADCS-ADL-MCI did favor lecanemab in the APOE ε4 homozygous subgroup, the effect size was attenuated compared to APOE ε4 noncarriers and ε4 heterozygotes.[50,51,53]

Safety
In Study 201, ARIA was observed in about 12% (20/161) of individuals treated with lecanemab 10 mg/kg biweekly compared to 5% (13/245) in the placebo arm. Respective incidences of ARIA-E were 10% (16/161) versus 1% (2/245) and ARIA-H was 6% (10/161) versus 5% (12/245). Symptomatic ARIA occurred in 3% (5/161) of individuals treated with lecanemab. Clinical symptoms associated with ARIA resolved in 80% of patients during the period of observation. The incidence of ARIA was higher in ApoE ε4 homozygotes than in heterozygotes and noncarriers among individuals treated with lecanemab. Of the 5 individuals treated with lecanemab who had symptomatic ARIA, 4 were ApoE ε4 homozygotes, 2 of whom experienced severe symptoms. While the recommendations on management of ARIA do not differ between ApoE ε4 carriers and noncarriers, as per the label, consider testing for ApoE ε4 status to inform the risk of developing ARIA when deciding to initiate treatment with lecanemab.[51]

In Study 301 (Clarity AD), deaths were reported in 0.7% of the participants in the lecanemab group versus 0.8% in the placebo group. ARIA was observed in 21% (191/898) of individuals treated with lecanemab compared to 9% (84/897) of individuals who received placebo. Symptomatic ARIA occurred in 3% (29/898) of individuals treated with lecanemab. Serious symptoms associated with ARIA were reported in 0.7% (6/898) of individuals treated with lecanemab. ARIA-E was observed in 13% (113/898) of individuals treated with lecanemab compared with 2% (15/897) on placebo. ARIA-H was observed in 17% (152/898) of individuals treated with lecanemab compared with 9% (80/897) on placebo. Clinical symptoms resolved in 92% of individuals with symptomatic ARIA-E and in 73% of individuals with symptomatic ARIA-H within the period of observation. Intracerebral hemorrhage (greater than 1 cm in diameter) was reported in 0.7% (6/898) of individuals on lecanemab compared to 0.1% (1/897) on placebo. Infusion-related reactions were reported in 26% (237/898) of individuals treated with lecanemab compared to 7% (66/897) of patients on placebo. ARIA incidence was higher in APOE ε4 homozygotes (45% on lecanemab vs 22% on placebo) compared to heterozygotes (19% on lecanemab vs 9% on placebo) and noncarriers (14% on lecanemab vs 4% on placebo). Of the individuals treated with lecanemab who experienced symptomatic ARIA, 45% were ApoE ε4 homozygotes, 41% were heterozygotes, and 14% were noncarriers. Serious events of ARIA occurred in 3% of ApoE ε4 homozygotes, and approximately 1% of heterozygotes and noncarriers.[51,53]

In the open label extension of Study 301, there were 3 deaths related to ARIA for which a role for lecanemab cannot 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 (CAA); one of which also was administered tPA.[5]

Donanemab

The efficacy of KISUNLA was evaluated in a double-blind, placebo-controlled, parallel-group study (Study 1, NCT04437511) in patients with Alzheimer's disease (patients with confirmed presence of amyloid pathology 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 were included in the study 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. Patients could enroll in an optional, long-term extension.

In Study 1, 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.

Additionally, 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 noncarriers. Fifty-seven percent of patients were female, 91% were White, 6% were Asian, 4% were Hispanic or Latino, and 2% were Black or African American.

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 (ADCSiADL) 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 (CDR-SB), 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) (see Table 8). There were also statistically significant differences (p<0.001) between treatment groups as measured by ADAS-Cog13 and ADCS-iADL at Week 76 (*see* Table 8).

Table 8: Efficacy Analysis Results in Combined Population at Week 76[a]

Clinical Endpoints	**KISUNLA (N = 860)**	**Placebo (N = 876)**
CDR-SB[b]		
Mean baseline	3.92	3.89
Adjusted mean change from baseline	1.72	2.42
Difference from placebo (%)[d]	-0.70 (29%) p<0.0001	-

ADAS-Cog$_{13}$[c]		
Mean baseline	28.53	29.16
Adjusted mean change from baseline	5.46	6.79
Difference from placebo (%)d	-1.33 (20%) p=0.0006	-
ADCS-iADL[c]		
Mean baseline	47.96	47.98
Adjusted mean change from baseline	-4.42	-6.13
Difference from placebo (%)d	1.70 (28%) p=0.0001	

a. Abbreviations: ADAS-Cog13 = Alzheimer's Disease Assessment Scale – 13-item Cognitive Subscale; ADCS-iADL = Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale; CDR-SB = Clinical Dementia Rating Scale – Sum of Boxes; NCS2 = natural cubic spline with 2 degrees of freedom; MMRM = mixed model for repeated measures.
b. Assessed using MMRM analysis. Assessed using NCS2 analysis.
c. d Percent slowing of decline relative to placebo: difference of adjusted mean change from baseline between treatment groups divided by adjusted mean change from baseline of placebo group 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 donanemab is stopped. There is no data beyond the 76-week duration of Study 1 to guide whether additional dosing with KISUNLA may be needed for longer-term clinical benefit.

12.2 Pharmacodynamics

Effect of KISUNLA on Amyloid Beta Pathology

The effect of KISUNLA on amyloid beta plaque levels in the brain was evaluated using amyloid Positron Emission Tomography (PET) imaging (^{18}F-florbetapir tracer). The PET signal was quantified using the Standard Uptake Value Ratio (SUVR) method to estimate brain levels of amyloid beta plaque in composites of brain areas expected to be widely affected by Alzheimer's disease pathology (precuneus, frontal, anterior cingulate, posterior cingulate, parietal, and temporal cortices), compared to a brain region expected to be spared of such pathology (cerebellum). Results of amyloid PET were also expressed on the Centiloid scale.

In Study 1, NCT0443751 1, KISUNLA reduced amyloid beta plaque levels in the brain in a time-dependent manner, starting at Week 24, and continuing through Week 76 (p<0.0001), compared to placebo (see Table 7). In clinical pharmacology studies, KISUNLA demonstrated a dose-and time-dependent reduction in amyloid beta plaque, with the decrease observed starting at Week 12.

Effect of KISUNLA on Tau Pathophysiology

A reduction in plasma p-tau217 was observed with KISUNLA compared to placebo in Study 1

Table 7: Biomarker Results of KISUNLA in Study 1

Biomarker Endpoint at Week 76	**KISUNLA**	**Placebo**
Amyloid Beta PET SUVR	**N = 712**	**N = 754**
Mean baseline	1.53	1.52
Adjusted mean change from baseline	-0.47	-0.00
Difference from placebo	-0.47, p<0.0001	
Amyloid Beta PET Centiloid	**N = 765**	**N = 812**
Mean baseline	104.0	101.8
Adjusted mean change from baseline	-87.0	-0.7
Difference from placebo	-86.4, p<0.0001	
Plasma p-tau217 (log10 transformed)[a]	**N = 758**	**N = 786**

Mean baseline	0.67	0.66
Adjusted mean change from baseline	-0.19	0.03
Difference from placebo	-0.22, p<0.0001	

N is the number of patients with baseline value.
a. Results should be interpreted with caution due to the uncertainties in bioanalysis.

Safety
The safety of KISUNLA has been evaluated in 2885 patients with Alzheimer's disease who received at least one dose of KISUNLA intravenously. In the clinical studies of KISUNLA, 1912 patients with Alzheimer's disease received KISUNLA once monthly for at least 6 months, 1057 patients for at least 12 months, and 432 patients for at least 18 months, at the recommended dosing schedule.

In Study 1 (NCT04437511), a total of 853 patients with Alzheimer's disease received at least one dose of KISUNLA.

Thirteen percent of patients treated with KISUNLA compared to 4% of patients on placebo stopped study treatment because of an adverse reaction. The most common adverse reaction leading to discontinuation of KISUNLA was infusion-related reaction (4% of patients treated with KISUNLA compared to no patient on placebo).

Table 6 shows adverse reactions that were reported in at least 5% of patients treated with KISUNLA and at least 2% more frequently than in patients on placebo in Study 1.

Adverse Reaction	KISUNLA N = 853 %	Placebo N = 874 %
ARIA-H microhemorrhagea	25	11
ARIA-E	24	2
ARIA-H superficial siderosis[a]	15	3
Headache	13	10
Infusion-related reaction	9	0.5

[a] As assessed by MRI. A participant could have both microhemorrhage and superficial siderosis.

Individual Consideration

All our medical policies are written for the majority of people with a given condition. Each policy is based on medical science. For many of our medical policies, each individual's unique clinical circumstances may be considered in light of current scientific literature. Physicians may send relevant clinical information for individual patients for consideration to:

Blue Cross Blue Shield of Massachusetts
Pharmacy Operations Department
25 Technology Place
Hingham, MA 02043
Tel: 1-800-366-7778
Fax: 1-800-583-6289

Policy History

Date	Action
10/2024	Policy clarified to include that per label, Donanemab is administered every four weeks as an intravenous infusion over approximately 30 minutes. Product label of donanemab recommends obtaining an MRI prior to the second, third, fourth, and seventh infusions.
8/2024	Policy clarified to: 1. add medically necessary and investigational indications for Donanemab (Kisunla). Effective 8/1/2024. 2. remove Aducanumab (Aduhelm). This drug has been discontinued. Code J0172 Injection, aducanumab-avwa, 2 mg transferred to MP 400 Medical Technology Assessment Non-Covered List. Effective 8/1/2024.

6/2024	Policy revised to include medically necessary and investigational indications for Leqembi (lecanemab). Effective 6/1/2024.
8/2023	Policy clarified to remove reference to Medicare from the commercial policy. Medicare policy is followed for Medicare Advantage members.
7/2023	Reformatted Policy.
4/2023	Updated to add Leqembi (lecanemab) to the policy as investigational.
8/2021	New medical policy describing investigational indications. The use of aducanumab is considered investigational for all indications including treatment of Alzheimer disease. Effective 8/1/2021.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

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