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P&T Date: 04/16/2026

Kisunla™ (donanemab-azbt)

HCPCS: J0175

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Commercial Benefit

- a. Coverage of the requested drug will be considered investigational/experimental for all indications due to insufficient evidence of a clinical benefit

***Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at <http://www.cms.hhs.gov/>. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Background Information:

- Alzheimer's disease is a progressive disease, with pathophysiological changes and clinical manifestations occurring along a continuum. It continues to be a growing health crisis worldwide, affecting patients with the disease and their families. Approximately 7.2 million Americans aged 65 years and older are currently living with Alzheimer's dementia. About 5 million individuals 65 years of age and older may have mild cognitive impairment (MCI) due to Alzheimer's disease, presenting as memory loss and confusion that does not interfere with activities of daily living; however, it may also be secondary to other conditions.
- It is estimated that 10-15% of individuals with MCI go on to develop dementia each year. Within 5 years, approximately 32% of patients with MCI due to Alzheimer's disease progress to dementia. The progression from MCI to dementia marks the point at which the symptoms of Alzheimer's disease will have gradually led to behavior and personality changes, a decline in cognitive abilities that interfere with a person's ability to carry out daily activities independently, and eventually more severe loss of mental function and problems recognizing family and friends. Diagnosis of MCI and of Alzheimer's dementia is based on clinical evaluation determining cognitive and functional status and not solely on test scores, with progressive cognitive decline demonstrated on subsequent follow ups with the patient.

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- Historically, only symptomatic therapies have been available for treating Alzheimer's dementia. These agents do not act on the evolution of the disease. Standard medical treatment for Alzheimer's disease dementia includes cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and N-methyl-D-aspartate (NMDA) antagonists (memantine).
- All cholinesterase inhibitors are approved for use in mild and moderate Alzheimer's dementia, though donepezil and transdermal rivastigmine are also approved to treat severe Alzheimer's dementia. Memantine, however, is not recommended in mild disease and is only approved for patients with moderate to severe Alzheimer's dementia.
- Current research efforts are focused on identifying and treating patients as early as possible for the best chance of slowing or stopping the progression of Alzheimer's disease. The accumulation of amyloid beta plaques is a defining pathophysiological feature of Alzheimer's disease that can be exhibited as early as the MCI stage of disease and potentially even earlier, before symptoms arise; as such, a great deal of research has focused on clearing amyloid beta from the brain early in the disease process in an attempt to affect disease progression.
- The presence of amyloid beta plaques can be confirmed by an amyloid positron emission tomography (PET) scan or a cerebrospinal fluid (CSF) test via lumbar puncture; these are the longest-standing FDA-cleared methods to confirm amyloid pathology. More recently in May 2025, the FDA cleared the first blood-based biomarker (BBM) test to detect amyloid plaques associated with Alzheimer's disease. Confirmation of the presence of amyloid pathology and other Alzheimer's disease biomarkers has not historically been guideline recommended for the diagnosis of Alzheimer's disease at any point in the disease process, and testing for these biomarkers has primarily been used for research and in settings where the use of FDA-approved therapies requires confirmation of their presence.
 - Amyloid PET imaging uses a class of radiopharmaceuticals that detect levels of amyloid in the human brain; examples of such radiopharmaceuticals include Amyvid™ (florbetapir F18), Neuraceq™ (florbetaben F18) and Vizamy™ (flutemetamol F18). These scans can be interpreted as positive (elevated amyloid) or negative (non-elevated amyloid). If the amyloid PET is positive with abnormal amyloid beta pathology present, cognitive and/or functional testing is necessary to assist in confirming and staging Alzheimer's disease. A positive amyloid PET alone is not diagnostic of Alzheimer's disease.
 - CSF testing measures beta-amyloid, specifically beta-amyloid 1-42 which is a marker of amyloid plaques, and total-tau (tTau) and phosphorylated-tau (pTau181) which are markers of neurofibrillary tangles and provide insight into the intensity of neurodegeneration. CSF testing can be useful in differential diagnosis of Alzheimer's disease and other causes of cognitive impairment. In contrast to amyloid PET scans which are typically high cost and limited in availability, the use of CSF assays offers the potential to provide a more affordable and more accessible option to verify amyloid pathology in the brain, as well as detection of both amyloid and tau biomarkers at once.
 - Elevated CSF levels of tTau and pTau181 are associated with faster progression of cognitive decline.
 - There are currently three CSF tests cleared by the FDA for the evaluation of Alzheimer's disease: 1) Lumipulse® G β-Amyloid Ratio (1-42/1-40) test, 2) Elecsys® beta-Amyloid (1-42) CSF II (Abeta42) and Elecsys® Phospho-Tau (181P) CSF (pTau181) assays (used as a pTau181/Abeta42 ratio), and 3) Elecsys® beta-Amyloid (1-42) CSF II (Abeta42) and Elecsys® Total-Tau (tTau) CSF assays (used as a tTau/Abeta42 ratio). Refer to Appendix 1 for additional information regarding these tests.
 - As with the amyloid PET, a positive result on CSF test alone is not diagnostic of Alzheimer's disease.

- BBM tests for Alzheimer's disease pathology provide a less invasive, more accessible alternative to amyloid PET and CSF testing. To date, there are two FDA approved BBM tests for Alzheimer's disease: Lumipulse G pTau217/ β -Amyloid 1-42 Plasma Ratio and Elecsys pTau181 plasma test. Refer to Appendix 2 for additional information.
- The Lumipulse G pTau217/ β -Amyloid 1-42 Plasma Ratio is approved for the early detection of amyloid plaques associated with Alzheimer's disease in adults aged 50 years and older exhibiting signs and symptoms of the disease. The test is intended for patients presenting in specialized care settings with demonstrable symptoms and signs of cognitive decline and, as with amyloid PET and CSF testing, must be interpreted in conjunction with other clinical information.
 - A clinical study comparing the Lumipulse G pTau217/ β -Amyloid 1-42 Plasma Ratio with amyloid PET scan or CSF test results showed 91.7% of individuals with Lumipulse G pTau217/ β -Amyloid 1-42 Plasma Ratio positive results had the presence of amyloid plaques by PET scan or CSF test, and 97.3 % of individuals with negative results had a negative amyloid PET scan or CSF test result. Based on this, the FDA found that the Lumipulse G pTau217/ β -Amyloid 1-42 Plasma Ratio is substantially equivalent to the Lumipulse G β -amyloid Ratio (1-42/1-40) CSF test.
- In October 2025, the FDA approved Roche's Elecsys pTau181 plasma test, the only BBM test indicated to aid in the initial assessment of AD and other causes of cognitive decline in the primary care setting. It is approved for patients 55 years of age and older presenting with signs, symptoms, or complaints of cognitive decline. The test measures pTau 181 protein, one of the key markers of amyloid plaque and tau aggregate pathology, and is intended to rule out AD-related pathology in conjunction with other clinical information and assessments.
 - FDA clearance of Elecsys pTau181 was supported by a non-interventional clinical study in an early disease-stage, low-prevalence population reflective of what is commonly seen in primary care. Among the 312 participants, the test ruled out Alzheimer's pathology with a 97.9% negative predictive value.
- The Alzheimer's Association's clinical practice guideline on the use of blood-based biomarkers in the diagnostic workup of suspected Alzheimer's disease within specialized care settings (2025) recommends the following in patients with objective cognitive impairment presenting for specialized memory-care. They do not endorse specific tests and caution that there is significant variability in diagnostic test accuracy and many commercially available BBM tests do not meet the recommended thresholds.
 - Using a BBM test with >90% sensitivity and >75% specificity for initial triage in the diagnostic workup of AD (conditional recommendation, low certainty evidence). A negative finding rules out amyloid pathology and a positive result requires confirmatory testing with amyloid PET or CSF biomarker analysis.
 - Using a high-sensitivity (> 90%) and high-specificity (> 90%) BBM test as a confirmatory test in the diagnostic workup of Alzheimer's disease (conditional recommendation, low certainty evidence). BBM testing that meets these thresholds may serve as a substitute for amyloid PET imaging or CSF biomarker testing. Negative results rule out AD pathology while positive results rule in AD pathology

- Updated criteria for the diagnosis and staging of Alzheimer's disease from the Alzheimer's Association Workgroup (2024) and the Alzheimer's Association's clinical practice guideline on the use of blood-based biomarkers in the diagnostic workup of suspected Alzheimer's disease within specialized care settings (2025) support a biologically based diagnosis of Alzheimer's disease using the above biomarkers, with the caveat that their use in clinical settings is for the evaluation of symptomatic individuals, and not those who are cognitively unimpaired. Additionally, the guidelines acknowledge that though the presence of abnormal biomarkers may be sufficient to confirm Alzheimer's pathology in a symptomatic individual, it should not preclude a clinician from exercising their clinical judgment and searching for other contributors to the patient's symptoms.
- Amyloid pathology can also be found in both cognitively unimpaired adults and in patients with other neurodegenerative disorders; therefore, a positive amyloid PET and/or CSF result alone may be insufficient to establish a diagnosis of Alzheimer's disease or other cognitive disorders. Results from these tests should be interpreted in tandem with other clinical diagnostic evaluations, including cognitive and/or functional testing.
- Validated mental and functional status exams are important tools for assessing cognitive and behavioral functions and measuring activities of daily living and are frequently used when screening older adults for MCI or dementia. They represent a portion of the necessary workup for cognitive impairment or dementia and, like biomarker evaluations, should be interpreted in the context of other clinical information prior to finalizing a diagnosis. Two of the most widely used mental status scales include the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA), while the Functional Activities Questionnaire (FAQ) is a commonly used functional status exam.
 - The MMSE evaluates temporal and spatial orientation, memory, attention/concentration, language, and visuospatial function. It is scored on a 30-point scale with scores <24 typically regarded as abnormal and indicative of cognitive impairment. Of note, age, education, and race/ethnicity have been shown to affect MMSE scores and should be considered when evaluating an individual patient.
 - The MoCA includes a broader range of cognitive domains, particularly executive abilities, and is able to detect more subtle cognitive deficits that characterize MCI. It evaluates delayed word recall, visuospatial/executive function, language, attention/concentration, and orientation. The MoCA is also scored on a 30-point scale, with scores of 18-25 suggestive of MCI. The cut-off score of 18 is usually considered to separate MCI from Alzheimer's disease, though there is overlap in the scores as AD is determined by the presence of cognitive impairment as well as the loss of functional independence.
 - The FAQ is a subjective 10-item scale that assesses a patient's functional abilities, specifically instrumental activities of daily living (IADL; e.g., preparing meals, performing chores, running errands, traveling outside of one's neighborhood, keeping track of finances). Per-item scores range from 0-3, with higher scores indicating greater functional impairment. There is no established cut-off score for IADL impairment, though a cut point of 9 (i.e., dependent in 3 or more activities) is recommended to indicate impaired function and possible cognitive impairment. The total FAQ score may be useful in differentiating MCI and mild Alzheimer's dementia.
- The Clinical Dementia Rating Scale (CDR) is another validated clinical instrument used to assess and standardize Alzheimer's disease staging that is most often used in research settings and is commonly used to stage dementia progression over time. It is derived from the scores in each of six different categories, or "box scores": memory, orientation, judgment, community affairs, home hobbies, and personal care. Memory is considered the primary category while all others are secondary. According to the CDR Global scores, Alzheimer's disease stages can be defined as unimpaired cognition (CDR Global = 0), MCI due to Alzheimer's (CDR Global = 0.5), mild Alzheimer's dementia (CDR Global = 1), moderate Alzheimer's dementia (CDR Global = 2), and severe Alzheimer's dementia (CDR = 3). If the memory box score is 0.5, the CDR Global score can only be 0.5 or 1.

- Ruling out other conditions with similar presentation is essential during diagnostic workup for a patient being evaluated for Alzheimer's disease. Examples of situations where a diagnosis of Alzheimer's disease may be unlikely are listed below; these examples are not all-inclusive. Additionally, when feasible and medically appropriate, patients should be weaned from medications that may contribute to cognitive impairment.
 - Evidence of concomitant cerebrovascular disease, defined by a history of stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden,
 - Features of Lewy Body dementia other than the dementia itself,
 - Prominent features of behavioral variant frontotemporal dementia,
 - Prominent features of semantic variant primary progressive aphasia or non-fluent/agrammatic variant primary progressive aphasia
 - Evidence for another neurological disease or a non-neurological medical comorbidity (e.g., HIV dementia, dementia of Huntington's disease) or medication use that could have a substantial effect on cognition.
 - Vitamin B12 or folate deficiency
 - Psychiatric diagnoses or symptoms, such as hallucinations, anxiety, major depression, or delusions
- The first FDA approved treatment for Alzheimer's disease that could potentially modify the disease process was Aduhelm® (aducanumab-avwa), a human immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta protein, for the treatment of Alzheimer's disease in patients with mild forms of Alzheimer's disease (i.e., MCI due to Alzheimer's or mild Alzheimer's dementia) as this was the population treated in clinical trials and no safety and effectiveness data is available on initiating treatment in earlier or later stages of the disease than were studied. Aduhelm was approved on June 7, 2021, and brought a first-in-class product to market. However, Aduhelm was approved via the accelerated approval pathway based on the reduction in amyloid beta plaques observed in clinical trials; discordant results of Aduhelm's identically designed Phase III EMERGE and ENGAGE trials failed to provide sufficient evidence to support that the lowering of beta amyloid plaque yields a clinical benefit of improved cognition and delayed disease progression. As such, Aduhelm has had minimal impact on the Alzheimer's population in the time since its approval due to uncertain clinical efficacy, negative press surrounding its approval, and questionable long-term safety, and was discontinued in November 2024.
- On January 6, 2023, the FDA granted Biogen/Eisai's Leqembi® (lecanemab-irmb) accelerated approval based on amyloid plaque reduction, making it the second humanized IgG1 monoclonal antibody directed against amyloid beta for the treatment of Alzheimer's disease. On July 6, 2023, the FDA granted full approval to Leqembi for the treatment of AD in patients with MCI or mild dementia stage of disease and confirmed presence of amyloid, the population in which treatment was initiated in clinical trials. The conversion to full approval was supported by data from the Phase III, randomized, placebo-controlled Clarity AD trial that demonstrated the drug's clinical benefit as it relates to amyloid reduction.
 - Clarity AD was conducted over 18 months in patients 50 to 90 years of age with early Alzheimer's disease (i.e., MCI due to Alzheimer's or mild Alzheimer's dementia) and evidence of amyloid on PET or by CSF testing (n=1,795). The primary endpoint was the change from baseline at 18 months in the score on the Clinical Dementia Rating Sum of Boxes (CDR-SB; range, 0-18 with higher scores indicating greater impairment), which assesses three domains of cognition (memory, orientation, judgment/problem solving) and three domains of function (community affairs, home/hobbies, personal care). Key secondary endpoints

included change in amyloid burden on PET and the scores on a variety of other cognitive and functional assessment scales.

- Participants treated with Leqembi demonstrated a statistically significant 27% less decline in CDR-SB compared to placebo at 18 months, with a mean difference of -0.45 ($p < 0.001$). Other measures of cognition assessed in the trial also showed statistically significant differences favoring the lecanemab treatment arm. It should be noted that statistical significance in the change in CDR-SB may not demonstrate a clinically important change, as some experts suggest that the minimum clinically important difference (MCID) in CDR-SB where a clinically meaningful change to patients, caregivers or clinicians is apparent is generally a change of 1 to 2 points.
- Change in amyloid burden on PET, another key secondary endpoint, was assessed in a substudy involving 698 participants. At 18 months, the lecanemab group demonstrated a statistically significant larger amount of beta amyloid removal compared with placebo, corresponding to a mean percentage difference of -76.0% ($p < 0.001$). 32.4% of those in the lecanemab arm reached amyloid negativity; however, it's worth noting that 7.8% of those in the placebo arm also were amyloid negative at 18 months.
- On July 2, 2024, the FDA approved Eli Lilly's Kisunla for the treatment of Alzheimer's disease, with the caveat that Kisunla should be initiated in patients with MCI or mild dementia stage of disease, the population in which treatment was initiated in the clinical trials. Kisunla marks the third FDA approved anti-amyloid therapy for early symptomatic Alzheimer's disease, and the second to gain full FDA approval based on demonstration of statistically significant clinical benefit in clinical trials alongside Leqembi. Kisunla targets a specific epitope of beta amyloid found within beta amyloid plaque to facilitate plaque removal. Of the approved anti-amyloid therapies, Kisunla is the first and only agent with evidence to support a limited-duration treatment regimen based on amyloid plaque removal, which could potentially result in fewer infusions and lower treatment costs.
- Approval of Kisunla was based on results from the double-blind, placebo-controlled, parallel-group, Phase III TRAILBLAZER-ALZ-2 trial. Participants ($n=1,736$) were required to have a diagnosis of MCI or mild dementia stage of Alzheimer's disease with confirmed presence of amyloid pathology based on amyloid PET imaging and a progressive change in memory function for at least 6 months. Eligible participants were also required to have the following during the screening period (i.e. within 63 days) prior to randomization:
 - An MMSE score ≥ 20 but ≤ 28
 - Baseline brain magnetic resonance imaging (MRI), without findings showing:
 - Increased risk for Amyloid-related imaging abnormalities (ARIA) and/or intracerebral hemorrhage (e.g., findings suggestive of ARIA-E and/or cerebral amyloid angiopathy (prior cerebral hemorrhage greater than 1 cm at greatest diameter, more than 4 cerebral microhemorrhages, more than 1 area of superficial siderosis, any macrohemorrhage or severe white matter disease) or other lesions (aneurysm, vascular malformation) that could potentially increase the risk of intracerebral hemorrhage
 - Presence of other clinically significant lesions that could indicate a dementia diagnosis other than Alzheimer's disease
- Additionally, those included in the study were required to have low/medium or high tau levels based on visual assessment of tau PET imaging, with tau levels considered prognostic of rate of clinical decline. Treatment effect was hypothesized to be more difficult to demonstrate in participants with high tau levels due to their more advanced disease state. Patients ranged from 59 to 86 years old, with a mean age of 73 years. Of the total trial population, 68% had low/medium tau level and 32% had high tau.

- Patients in TRAILBLAZER-ALZ-2 were randomized 1:1 to receive Kisunla (n=860) or placebo (n=876) for a total of up to 72 weeks. Patients who achieved a prespecified reduction in amyloid levels as measured by amyloid PET at weeks 24, 52, and 76 were switched to placebo. Analyses were conducted on two primary populations within the trial: the low/medium tau level population, and the combined population of low/medium plus high tau groups.
 - The primary endpoint was change in the integrated Alzheimer's Disease Rating Scale (iADRS) score from baseline to 76 weeks. The iADRS is a combination of the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog13) score, which assesses cognition, and the Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living (ADCS-iADL) scale score, which assesses function. The total score ranges from 0 to 144, with lower scores reflecting worse cognitive and functional performance. Other efficacy endpoints evaluated in the trial included the CDR-SB, the ADAS-Cog13, and the ADCS-iADL.
 - Patients treated with Kisunla demonstrated a statistically significant reduction in clinical decline on iADRS compared to placebo at week 76 in both the combined tau group (2.92, $p < 0.0001$) and the low/medium tau group (3.25, $p < 0.0001$), equating to a 22% slowing of disease progression at week 76 in the combined tau group and 35% slowing of disease progression at week 76 in the low-medium tau group.
 - Statistically significant reduction in clinical decline on CDR-SB compared to placebo at week 76 was also demonstrated in the combined tau group (-0.70, $p < 0.0001$) and the low/medium tau group (-0.67, $p < 0.0001$), correlating to a 29% slowing of disease progression at week 76 in the combined group and a 36% slowing of disease progression in the low/medium tau group. Statistically significant differences between treatment groups were also demonstrated as measured by ADCS-Cog13, and ADCS-iADL at week 76 ($p < 0.001$).
 - The percentages of patients that reached the prespecified reductions in amyloid and were 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. Of note, amyloid PET values could increase after Kisunla treatment is stopped, and there is no data beyond the 76-week trial to guide whether additional Kisunla dosing may be needed for longer-term clinical benefit or how long the amyloid reductions with treatment will last.
- With the approval of Kisunla, we now have two Phase III clinical trials of anti-amyloid therapies (i.e., Clarity AD and TRAILBLAZER-ALZ-2) that have demonstrated an association between amyloid clearance and slowing of cognitive decline in the early Alzheimer's patient population; however, the available evidence, particularly in light of the history of mixed results with previously trialed and failed anti-amyloid therapies in the pipeline, does not unequivocally suggest that amyloid clearance will definitively improve cognitive outcomes. It also remains unclear whether the modest effect on cognition and function demonstrated in the trial will be clinically relevant when used in the real world. There is disagreement among experts about clinical meaningfulness of the magnitude of change in the cognitive outcomes of these trials, and despite the demonstrated statistical significance of the reduction in cognitive decline, we cannot say with certainty that treatment with Kisunla and other anti-amyloid therapies will yield a meaningful change in the patient's status for the benefit to outweigh the risk to treatment. Ultimately, uncertainty remains around the amyloid hypothesis and we do not have adequate data for anti-amyloid therapies to show a correlation between amyloid removal and treatment effect, or differences in outcomes by achieving or not achieving amyloid negativity.
- Any cognitive benefits seen with Kisunla and other anti-amyloid therapies must be weighed against the potential harms of treatment, especially in light of the risk of amyloid-related imaging abnormalities (ARIA) with edema and/or cerebral microhemorrhage. We must also recognize that ARIA risk with real world use may be greater than that in clinical trials due to issues like limited clinical expertise and accessibility issues affecting monitoring. ARIA can occur spontaneously in patients with Alzheimer's disease, with the three main risk factors being exposure to anti-amyloid treatment, presence of pre-treatment microhemorrhages, and APOE $\epsilon 4$ carrier status. Per the labeling, testing for

ApoE ε4 status is recommended prior to initiating treatment to inform the risk of ARIA development, though it is not a requirement. The prescriber should educate the patient on test results and its implications, including the risk of ARIA associated with APOE ε4 status. For those opting out of testing, the prescriber should inform patients they can still be treated with Kisunla; however, it cannot be determined if they are at higher risk for ARIA based on APOE ε4 status. The benefits of treatment versus the potential risk of ARIA should be considered prior to initiating treatment with Kisunla. An FDA-authorized test to detect ApoE ε4 alleles to identify those at risk of ARIA is not currently available, and those that are available may vary in accuracy and design.

- Caution should also be exercised when considering administration of Kisunla in patients with factors indicating increased risk of intracerebral hemorrhage, in particular those who need concomitant anticoagulant therapy, as well as when considering the administration of antithrombotics or a thrombolytic agent (e.g., tissue plasminogen activator) to a patient already being treated with Kisunla. Because ARIA-E can cause focal neurologic deficits that can mimic an ischemic stroke, treating clinicians should consider whether such symptoms could be due to ARIA-E before giving thrombolytic therapy in a patient being treated with Kisunla.
 - Patients with a history of transient ischemic attacks (TIAs) or stroke within the previous 12 months and those with an inadequately controlled bleeding disorder (including platelet count <50,000 or International Normalized Ratio [INR] >1.5) were not eligible to participate in Leqembi clinical trials in early Alzheimer's disease. Given that these factors may increase the risk of intracerebral hemorrhage in this patient population, it is clinically appropriate to apply the same exclusions to Kisunla and other future anti-amyloid therapies.
- The cognitive decline associated with MCI and mild Alzheimer's disease dementia often spans many years. The limited follow up duration of Kisunla's Phase III trial may be insufficient to conclude how effective Kisunla is for treating early Alzheimer's disease in the long term. Ultimately, longer trials are warranted to determine the true efficacy and safety of Kisunla in early Alzheimer's disease. With the lack of information surrounding long-term use, safety, and the real-world effects of Kisunla, a number of questions arise including the appropriate duration of treatment, if or at what point effectiveness will start to decline, and how discontinuation of Kisunla upon reaching undetectable levels of amyloid beta plaque will affect the trajectory of Alzheimer's disease progression.
- Shortly after Kisunla's approval, 36-month results from the open-label, long-term extension study (OLE) of Clarity AD were presented at the 2024 Alzheimer's Association International Conference (AAIC), with data appearing to support that Leqembi continues to work and maintain a similar slowing of cognitive decline as in the original 18-month trial, and that earlier treatment provides greater effect.
- At the 2025 AAIC, four-year results from Leqembi's Clarity AD OLE and 36-month results from Kisunla's TRAILBLAZER-ALZ2 long-term extension (LTE) were presented.
 - In the Clarity AD OLE, the mean change from baseline in CDR-SB in the Leqembi-treated group was -1.75 points after 48 months of treatment compared to a prespecified natural history cohort of Alzheimer's disease. The OLE also demonstrated a 34% reduction in the relative risk of progression to the next disease stage through 4 years of treatment. Additionally, the tau PET substudy of Clarity AD showed that after 4 years of Leqembi treatment, 69% of patients who had low tau levels showed improvement or no decline, and 56% showed improvement from baseline on CDR-SB global cognitive and functional scale.
 - The 4-year OLE data appear to demonstrate consistent benefits of continuous treatment with Leqembi. It should be noted that the 4-year data analysis varied from that conducted at 36 months in that only patients who had been established on Leqembi from inception of the Clarity AD trial were included in the data set.

- Of the 849 patients who had received Leqembi from the beginning of Clarity AD, roughly half had dropped out by the 48-month mark. It is unknown whether these patients experienced disease progression, intolerable side effects, or were lost to follow up due to some other factor. Those who are still enrolled may potentially be doing well because they are more actively managing their disease.
- Treated patients were again compared to historical data from untreated Alzheimer's patients in the Alzheimer's Disease Neuroimaging Initiative (ADNI). Use of a natural history cohort for comparison presents potential risks for bias and confounding. Additionally, neither the ADNI cohort nor either active treatment arm can be considered representative of the broader Alzheimer's population that would be treated in the real world.
- The TRAILBLAZER-ALZ 2 LTE included 550 patients who initiated Kisunla in the core study and either continued or were switched to placebo after reaching amyloid negativity. Those receiving placebo in the core study were switched to Kisunla for the LTE to evaluate delayed treatment outcomes (n=657).
 - Compared with the ADNI natural history cohort, Kisunla reduced cognitive decline by -0.6 at 18 months and then -1.2 at 36 months on the CDR-SB.
 - Earlier initiation of Kisunla reduced risk of progression to the next disease stage by 27% on the CDR-Global compared to patients with delayed initiation of Kisunla treatment.
 - More than 75% of participants reached amyloid clearance within 76 weeks of starting Kisunla.
 - After up to 2.5 years of observed data in patients who had completed Kisunla treatment, accumulation of amyloid plaque remained slow.
 - The LTE data appears to support that Kisunla continues to provide clinical benefit even after discontinuation of therapy and that earlier treatment provides a more pronounced treatment effect. Caveats to consider when interpreting this data are similar to those of Clarity AD OLE and include that the LTE compared the progression of treated patients to data from a natural history cohort of untreated patients in lieu of a placebo control group, which could potentially confound the results. Additionally, nearly half of patients in the early start Kisunla group dropped out of the study by 36 months for unknown reasons, and, as with Leqembi, those who are still enrolled may potentially be doing well because they are more actively managing their disease.
- Data appears supportive of chronic Leqembi treatment; however, with new data on Kisunla suggesting that patients can stop taking drug once they reach amyloid negativity and treatment benefit continues to grow, the question remains whether there is value, or lack thereof, in continuing treatment of anti-amyloid therapies post-plaque clearance. Controlled head-to-head studies directly comparing the different drugs and treatment regimens are needed to find a resolution to the conflicting conclusions drawn from these extension trials.
- The Centers for Medicare & Medicaid Services (CMS) recognizes the need for additional information surrounding treatment with Kisunla and other anti-amyloid therapies in the real world. On April 7, 2022, CMS released a national policy for coverage of monoclonal anti-amyloid antibodies approved by the FDA for the treatment of Alzheimer's disease. Under the National Coverage Determination (NCD), Medicare will only provide coverage of FDA approved anti-amyloid antibodies under Coverage with Evidence Development (CED) when furnished in accordance with prespecified coverage criteria laid out in the NCD for patients with a clinical diagnosis of MCI due to Alzheimer's disease or mild Alzheimer's disease dementia, both with confirmed presence of amyloid beta pathology consistent with Alzheimer's disease.

- Coverage of these anti-amyloid therapies under CED requires participation in CMS-approved prospective comparative studies, and providers must participate in an approved registry to gather information on patient outcomes with treatment to further evaluate whether these products are reasonable and necessary in the Medicare-eligible population. The data collected by these registries is expected to help answer such questions as whether Kisunla and other approved anti-amyloid therapies meaningfully improve health outcomes with real-world use, whether the benefits and harms of these therapies are dependent on select factors in a patient's care, and how the benefits and harms of treatment may change over time. A CED cycle is considered completed once CMS completes reconsideration of the CED coverage decision and the study participation requirement as a condition of coverage is removed. At this time, an analysis of the data collected by CMS for the early Alzheimer's population has not yet been made available to further inform decisions around the long-term use of anti-amyloid therapies.
- Refer to CMS's NCD: Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease for a complete description.
- To date, there is no literature available to support the use of Kisunla in combination with other anti-amyloid therapies.
- On June 10, 2024, the FDA's Peripheral and Central Nervous System Drugs Advisory Committee convened and unanimously voted 11-0 in favor of Kisunla, voting that the available data supported Kisunla's effectiveness in the population enrolled in clinical trials, which excluded patients with low or no tau burden, and that the benefits outweigh the risks of Kisunla in the treatment of Alzheimer's disease in the population enrolled in the clinical trials. Though the vote was unanimous, the committee recognized that questions remained around Lilly's decision to cease dosing once a patient achieved amyloid clearance, particularly with regard to how clinicians in the real world would monitor for and determine when to cease dosing, and they acknowledged that longer-term follow up would be beneficial to provide more clear guidance on both stopping treatment and potentially restarting. The committee also acknowledged that we lack answers to questions surrounding Kisunla's duration of benefit, how to monitor patients between drug stoppage and restarting, and what will happen with side effects in the interim or upon restarting treatment, and that data on patients within different subgroups was lacking, in particular the higher risk ApoE 4 homozygotes and those with little to no representation in the trial which lacked diversity.
- Appropriate use recommendations (AUR) for Kisunla were developed by the Alzheimer's Disease and Related Disorders Therapeutic Workgroup in 2025 to guide implementation of Kisunla use in real-world practice, prioritizing safety considerations and opportunity for effectiveness. The recommendations primarily align with the TRAILBLAZER-ALZ2 inclusion and exclusion criteria with slight variations, often erring more conservatively. AUR include, but are not limited to, the following:
 - Appropriate candidates for Kisunla include patients with MCI or mild dementia due to Alzheimer's disease (Clinical Stage 3 or 4, respectively) with biomarker confirmation of amyloid via PET or CSF testing. CSF biomarker ratios and amyloid PET are considered equivalent in terms of accuracy and performance, and the choice of test may be driven by access concerns or patient preference.
 - No BBM tests were FDA approved at the time of AUR publication, and clinical experience and performance in real-world populations were noted as not yet well established. The AUR therefore do not recommend establishing treatment eligibility solely on a positive blood biomarker test; however, in the advent of BBM test approval, the AUR anticipates that these tests will meet appropriate performance criteria to be considered appropriate for establishing eligibility for treatment with Kisunla and other anti-amyloid therapies for Alzheimer's disease.
 - APOE genotyping should be performed to inform risk of ARIA development.

- Pre-treatment MRI should be obtained within at most 12 months and ideally less than 6 months of treatment initiation. Those unable to undergo MRI would not be eligible for Kisunla treatment.
- The AUR recommend against using Kisunla in patients receiving anticoagulants, including warfarin, heparin, and direct oral anticoagulants, until additional safety data are available.
- It is reasonable for clinicians to consider discontinuing treatment if amyloid clearance is demonstrated by a negative amyloid PET, typically obtained 12-18 months post-treatment initiation. The rationale for limited treatment duration is based on Kisunla's selectivity for insoluble, mature plaques imaged by PET. Only amyloid PET is validated to assess amyloid plaque clearance in response to treatment; however, the Work Group acknowledges that knowledge gaps exist around the ability to implement amyloid PET-based stopping rules for Kisunla in clinical practice.
- Based on the current information available, there is insufficient evidence that Kisunla provides a meaningful clinical benefit in patients with mild Alzheimer's disease, and that potential benefits of therapy outweigh the risks of treatment. Therefore, further demonstration of clinical benefit and safety is warranted.

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Policy History												
#	Date	Change Description										
1.6	Effective Date: 04/16/2026	For commercial benefit, removed bullet stating that BCBSM/BCN is awaiting results of ongoing clinical trials since Kisunla has full FDA approval Changed Medicare criteria to “Coverage of the requested drug will be provided in accordance with CMS’s National Coverage Determination: Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer’s Disease” and removed corresponding quantity limits, authorization period, and renewal criteria Updating supporting information to include Elecsys p-Tau181 plasma test and Appendix 2: Blood Biomarker Tests Cleared by the FDA for the Evaluation of Alzheimer’s Disease										
1.5	Effective Date: 10/09/2025	Added CSF testing as an option for confirming amyloid-beta pathology to Medicare criteria Expanded MRI time limits from within the past 60 days to within at most the past 12 months										
1.4	Effective Date: 02/13/2025	Added initial criteria, quantity limits, authorization period, and renewal criteria for Medicare benefit only										
1.3	Effective Date: 08/08/2024	New policy. This criteria replaces previously approved preliminary criteria.										
1.2	Effective Date: 07/18/2024	UM medical management system update for BCBS and BCN <table><tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr><tr><td>BCBS</td><td>Yes</td></tr><tr><td>BCN</td><td>Yes</td></tr><tr><td>MAPPO</td><td>Yes</td></tr><tr><td>BCNA</td><td>Yes</td></tr></table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	Yes	BCN	Yes	MAPPO	Yes	BCNA	Yes
Line of Business	PA Required in Medical Management System (Yes/No)											
BCBS	Yes											
BCN	Yes											
MAPPO	Yes											
BCNA	Yes											

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1.1	Effective Date: 08/10/2023	Updated proposed Medicare preliminary criteria to reference National Coverage Determination vs. National Coverage Analysis
1.0	Effective Date: 12/01/2022	Preliminary drug review

* The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or <http://dailymed.nlm.nih.gov/dailymed/index.cfm>.

Appendix 1: CSF Tests Cleared by the FDA for the Evaluation of Alzheimer's Disease (AD) Biomarkers*

Test	What is measured	Results Interpretation	Notes
Lumipulse β -Amyloid Ratio (1-42/1-40) Fujirebio Diagnostics, Inc.	Ratio of AB 1-42 and AB 1-40 concentrations Determines likelihood of amyloid plaques	Negative (normal): ≥ 0.073 Likely positive (abnormal): 0.059-0.072 Positive (abnormal): ≤ 0.058	AB 1-42 accumulation leads to plaque aggregation and neurotoxicity in AD AB 1-40 remains relatively stable and less prone to aggregating Likely positive and positive results are more likely to be consistent with a positive amyloid PET result; however, these results do not establish a diagnosis of AD or other cognitive disorders.
Elecsys beta-amyloid (1-42) CSF II and Elecsys Phospho-Tau (181P)CSF (pTau181) Roche	Used together to measure the ratio of pTau181 and AB 1-42 concentrations Ratio provides a surrogate marker of amyloid plaque burden with 90% concordance with Amyloid PET imaging	Negative (normal): ratio $\leq$ lab-designated ratio cut-off Positive (abnormal): ratio $>$ lab-designated ratio cut-off	Increases in CSF pTau181 concentration is associated with more rapid cognitive decline in AD Results below the cut-off reduces the likelihood of AD causing the cognitive impairment Intended to be used in addition to other clinical diagnostic evaluations.
Elecsys beta-amyloid (1-42) CSF II and Elecsys Total-Tau CSF Roche	Used together to measure the ratio of tTau and AB 1-42 concentrations Ratio provides a surrogate marker of amyloid plaque burden concordant with Amyloid PET imaging	Negative (normal): ratio $\leq$ lab-designated ratio cut-off Positive (abnormal): ratio $>$ lab-designated ratio cut-off	Expected to be available 4 th quarter 2023 High CSF tTau can also be found in other neurodegenerative disease (e.g., Creutzfeldt-Jakob disease) Intended to be used in addition to other clinical diagnostic evaluations.

AB – amyloid beta; pTau181 – phosphorylated tau-181; tTau – total Tau

*All are cleared by the FDA for adults 55 and older presenting with cognitive impairment who are being evaluated for AD and other causes of cognitive decline.

*Results from different assays may be different and cannot be used interchangeably.

*Results must be interpreted in conjunction with other diagnostic tools, such as neurological examination, neurobehavioral tests, imaging, routine lab tests.

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Appendix 2: Blood Biomarker Tests Cleared by the FDA for the Evaluation of Alzheimer's Disease (AD)*

Test	What is measured	Results Interpretation	Notes
Lumipulse G pTau217/β-Amyloid 1-42 plasma ratio Fujirebio Diagnostics, Inc.	Ratio of phosphorylated tau 217 to AB 1-42 The numerical ratio of the levels of these proteins correlates to the presence or absence of amyloid plaque, reducing the need for an amyloid PET with a 91.8% positive predictive value	Positive (abnormal): ratio ≥ 0.00738 Intermediate (uncertain): ratio 0.00371 – 0.00737 Negative: ratio ≤ 0.00370 (normal)	Intended for use in specialized care settings only, in adults age 50 years and older Not to be used as a screening or stand-alone diagnostic test. Results should be interpreted in conjunction with other pertinent clinical information Results are highly concordant with amyloid PET and amyloid CSF ratio results Patients with intermediate results are uncertain to have amyloid pathology and should consider further testing
Elecsys p-Tau181 Roche	Used to measure plasma levels of phosphorylated tau 181, a protein that increases as amyloid plaques accumulate in the brain A 97.9% negative predictive value for ruling out AD	Negative: ≤ 0.722 pg/mL (consistent with a negative amyloid PET scan; investigate for causes other than amyloid pathology) Positive: >0.722 pg/mL (may not be consistent with a positive amyloid PET; further investigation required to determine if amyloid is a cause)	Intended to aid in the initial assessment for AD in adults 55 years and older in the primary care setting. Not recommended for patients who are symptomatic and already referred to a specialist Results should be interpreted in conjunction with other clinical information A positive test result may not be consistent with a positive amyloid PET scan result. Patients with an initial positive result should be further investigated to determine whether the amyloid pathology can be a cause of cognitive impairment.

AB – amyloid beta

*Results must be interpreted in conjunction with other diagnostic tools, such as neurological examination, neurobehavioral tests, imaging, routine lab test

Blue Cross Blue Shield/Blue Care Network of Michigan

Medication Authorization Request Form



This form is to be used by participating physicians to obtain coverage for **drugs covered under the medical benefit**. For commercial members only, please complete this form and submit via fax to 1-877-325-5979. If you have any questions regarding this process, please contact BCBSM Provider Relations and Servicing or the Medical Drug Helpdesk at 1-800-437-3803 for assistance.

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PATIENT INFORMATION	PHYSICIAN INFORMATION
Name	Name
ID Number	Specialty
D.O.B. ☐ Male ☐ Female	Address
Diagnosis	City /State/Zip
Drug Name	Phone/Fax: P: () - F: () -
Dose and Quantity	NPI
Directions	Contact Person
Date of Service(s)	Contact Person Phone / Ext.

STEP 1: DISEASE STATE INFORMATION

- Is this request for: ☐ Initiation ☐ Continuation Date patient started therapy: _____
- Administered by patient or a medical professional? ☐ patient (self) ☐ health care professional (physician, nurse, etc.)
- Site of administration? ☐ Provider office/Home infusion ☐ Other: _____
☐ Hospital outpatient facility (go to #4) Reason for Hospital Outpatient administration: _____
☐ Hospital inpatient facility for Car-T therapy only (for example: Kymriah, Yescarta, or Tecartus) (go to #5)
- Please specify location of administration if hospital outpatient infusion: _____
- Please specify location of administration if hospital inpatient infusion: _____
- Please provide the NPI number for the place of administration: _____
- Initiation AND Continuation of therapy:**
 - What is the patient's diagnosis? _____
 - What other medication has the patient received for their condition? Please list _____
 - Please describe the response to previous therapies: _____
 - Will the patient be receiving any other treatment for the listed condition while on this medication? Please list: _____
 - Please list any labs values important for diagnosing or monitoring this patient's condition: _____
- Continuation of therapy:**
 - Has the patient progressed while on this medication? ☐ yes ☐ no
 - How has the patient's condition changed while on this medication?

☐ Improved: Please describe: _____
 ☐ Stable: please describe: _____
 ☐ Worsened; Please describe: _____
 ☐ Other; Please describe: _____

Chart notes are required for the processing of all requests. Please add any other supporting medical information necessary for our review (required)

Coverage will not be provided if the prescribing physician's signature and date are not reflected on this document.

☐ Request for expedited review: I certify that applying the standard review time frame may seriously jeopardize the life or health of the member or the member's ability to regain maximum function

Physician's Name	Physician Signature	Date
Step 2: Checklist	☐ Form Completely Filled Out ☐ Provide chart notes	☐ Attach test results
Step 3: Submit	By Fax: BCBSM Specialty Pharmacy Mailbox 1-877-325-5979	By Mail: BCBSM Specialty Pharmacy Program P.O. Box 312320, Detroit, MI 48231-2320

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7/26/2018, 9/18/2018; 1/31/2020; 3/17/2020; 8/9/2021