Blue Cross Blue Shield Blue Care Network of Michigan

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P&T Date: 02/13/2025

**Leqembi™** (lecanemab-irmb)

**HCPCS:** J0174

**Policy:**

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

A. Commercial Benefit:
   a. Coverage of the requested drug is considered investigational/experimental for all indications due to insufficient evidence of a clinical benefit.
      i. BCBSM and BCN are awaiting the results of ongoing clinical trials to provide evidence of a clinical benefit.

B. Medicare Benefit:
   Coverage of the requested drug will be provided when all of the criteria are met. Coverage requests must be supported by submission of chart notes and patient specific documentation.
   a. Diagnosis of early symptomatic Alzheimer's disease (AD) defined as mild cognitive impairment (MCI) or mild AD dementia as confirmed by ALL of the following:
      i. Confirmed amyloid-beta pathology based on at least one of the following:
         a) The presence of amyloid beta pathology consistent with AD confirmed by amyloid positron emission tomography (PET) scan, OR
         b) Cerebrospinal fluid (CSF) biomarker testing documents abnormalities suggestive of beta-amyloid accumulation in the brain (e.g., Aβ42: 40 ratio, p-tau/Aβ42)
      ii. Other differential diagnoses have been ruled out and/or adequately managed by their respective specialists including:
         a) Other types of dementia (e.g. vascular dementia, Lewy body dementia)
         b) Other medical and neurological causes of cognitive impairment (e.g. medications, infections, vitamin B12 deficiency, folate deficiency)
         c) Psychiatric diagnoses or symptoms (e.g. hallucinations, anxiety, major depression, or delusions)
      iii. Mildly impaired cognition as evidenced by Mini Mental State Exam (MMSE) score and/or Montreal Cognitive Assessment (MoCA) score results within the past two months
      iv. Global CDR score of 0.5 to 1.0 and a CDR Memory Box score of 0.5 or greater within the past two months.
   b. Brain magnetic resonance imaging (MRI) completed within the past 60 days without findings that indicate an increased risk for amyloid-related imaging abnormalities (ARIA) and/or intracerebral hemorrhage, including:

i. Findings suggestive of ARIA and/or cerebral amyloid angiopathy (prior cerebral hemorrhage greater than 1 cm at greatest diameter, more than 4 microhemorrhages, superficial siderosis, vasogenic edema) or other lesions (aneurysm, vascular malformation) that could potentially increase the risk of intracerebral hemorrhage.

c. Member is not currently taking an anticoagulant (e.g. warfarin, apixaban)
    i. If the member is currently taking an anticoagulant, the prescriber must attest that education has been provided that the use of anti-amyloid therapy with anticoagulant therapy may increase the risk of intracerebral hemorrhage
d. Testing for ApoE ε4 status has been completed and the prescriber attests that education has been provided on test results including the risk of ARIA associated with ApoE ε4 status if applicable
    i. If the member has opted out of testing, the prescriber must attest that the patient understands the risk versus benefit of treatment, including an increased risk of ARIA if positive for ApoE ε4
e. No documented history of any of the following:
    i. Transient ischemic attacks (TIA), stroke, or seizures within 12 months
    ii. Evidence of other clinically significant lesions on brain MRI at Screening that could indicate a dementia diagnosis other than AD
    iii. Presence of a bleeding disorder that is not under adequate control (including a platelet count <50,000 or International normalized ratio [INR] >1.5)
f. Member must be enrolled in an approved study/registry that meets the Centers for Medicare and Medicaid Services (CMS) Coverage with Evidence Development (CED) criteria and is listed on the 'Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (AD)' page of the CMS CED website
g. Not to be used in combination with other anti-amyloid therapy

C. Quantity Limitations, Authorization Period, and Renewal Criteria (Medicare Benefit Only)
    a. Quantity Limits: Align with FDA recommended dosing
    b. Authorization Period: Six months
    c. Renewal Criteria: For continuation of therapy, all of the following requirements must be met:
        i. Diagnosis of MCI or mild AD dementia as evidenced by Mini Mental State Exam (MMSE) score and/or Montreal Cognitive Assessment (MoCA) score results within the past three months
        ii. Follow up MRIs have been completed at the intervals indicated in the FDA package insert and either:
            a) ARIA has not been observed on MRI, OR
            b) ARIA has been observed on MRI and all of the following:
                1. The prescriber attests that continuation of therapy is appropriate based on the severity of the patient's clinical symptoms, AND
                2. Follow-up MRI demonstrates radiographic resolution and/or stabilization, OR the prescriber attests that continuation of therapy is appropriate based on the radiographic severity of ARIA

***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. Nearly 7 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.

    - 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 only two FDA-cleared methods to confirm amyloid pathology at this time. 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 Vizamyl™ (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.

- Updated guidelines from the Alzheimer's Association Workgroup (2024) 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 are. 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 = 0.3). 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, or

    - 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 delusion

- 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 November 2024.

- On January 6, 2023, the FDA approved Leqembi (lecanemab-irmb) via the accelerated approval pathway as the second humanized IgG1 monoclonal antibody directed against amyloid beta for the treatment of Alzheimer's disease based on amyloid plaque reduction in a Phase II clinical trial, with continued approval contingent upon verification of a clinical benefit in a confirmatory trial. Leqembi is limited to treating patients with MCI due to Alzheimer's or mild Alzheimer's dementia and confirmed presence of amyloid as this was the population evaluated in clinical trials, and no safety or effectiveness data is available on initiating treatment earlier or later in the disease course.

    - Study 201, a Phase II, double-blind, placebo-controlled, dose-finding study of Leqembi in patients with early Alzheimer's disease, served as the basis for FDA's accelerated approval of Leqembi. Study 201 had a 79-week, double-blind, placebo-controlled period, followed by an open-label, extension for up to 206 weeks which was initiated after a gap period of treatment that ranged from 9 to 59 months.

    - The study included patients with MCI due to Alzheimer's disease or mild Alzheimer's dementia and confirmed presence of amyloid pathology (n=856). Participants were randomized to receive one of five doses of Leqembi or matched placebo, with 161 patients randomized to the 10 mg/kg every 2 weeks treatment arm.

    - The Leqembi treatment arms did not meet the primary endpoint of Study 201, which was a change from baseline on a composite score consisting of selected items from various cognitive function tests at week 53. However, those who voluntarily enrolled in the amyloid PET substudy (n=315) and received Leqembi treatment demonstrated significant dose- and time-dependent reduction of amyloid beta plaque from baseline compared to placebo at week 79.

- 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 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 cerebrospinal fluid (CSF) testing (n=1,795). Eligible participants were also required to have all of the following during the screening and/or baseline period (i.e., within 60 days) prior to randomization:

        - A global Clinical Dementia Rating (CDR) score of 0.5 (for MCI due to Alzheimer's) or 0.5 – 1.0 (for mild Alzheimer's dementia), and a CDR Memory Box score of 0.5 or greater

        - An MMSE score > 22 but < 30

        - Baseline brain magnetic resonance imaging (MRI), without findings that indicate increased risk for Amyloid-related imaging abnormalities (ARIA) and/or intracerebral hemorrhage (e.g., findings suggestive of ARIA and/or cerebral amyloid angiopathy (prior cerebral hemorrhage greater than 1 cm at greatest diameter, more than 4 microhemorrhages, superficial siderosis, vasogenic edema) or other lesions (aneurysm, vascular malformation) that could potentially increase the risk of intracerebral hemorrhage

    - Participants were excluded from Clarity AD if their history included any of the following:

        - History of transient ischemic attacks (TIA), stroke, or seizures within the previous 12 months

- Evidence of other clinically significant lesions on brain MRI at screening that could indicate a dementia diagnosis other than AD

- Presence of a bleeding disorder that is not under adequate control (including a platelet count <50,000 or International normalized ratio [INR] >1.5)

- Participants were randomly assigned (1:1) to receive Leqembi 10 mg/kg IV every 2 weeks or matched placebo. 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). 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 ($p<0.001$). 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.

- The other measures of cognition assessed in the trial also showed statistically significant differences favoring the lecanemab treatment arm; however, the mean differences in these endpoints also did not meet the MCID established by literature or as calculated by the Institute for Clinical and Economic Review (ICER).

- Changes 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.

- Clarity AD was the first clinical trial of an anti-amyloid therapy to demonstrate 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.

- Any cognitive benefits seen with Leqembi 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. Though the incidence of ARIA was numerically lower with Leqembi than with other anti-amyloid therapies in similar clinical trials, the differences in the drugs used and trial design do not allow direct comparisons or support the suggestion that Leqembi may be "safer" than alternative anti-amyloid agents previously studied.

- With the FDA's full approval of Leqembi came the application of a boxed warning regarding ARIA, calling out ApoE ε4 homozygotes in particular who appear to have a higher incidence of ARIA, including symptomatic, serious, and severe radiographic ARIA, compared to heterozygotes and noncarriers. 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 ε4 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

Leqembi; 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 Leqembi. 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 Leqembi in patients receiving concomitant antithrombotic or thrombolytic medications. Use of these medications (e.g., aspirin, other antiplatelets, anticoagulants) was allowed in Clarity AD if the patient was stable on the dose; however, there was a greater incidence of intracerebral hemorrhage in patients taking Leqembi with antithrombotic (2/79 patients) compared to those receiving placebo (zero patients).

- The cognitive decline associated with MCI and mild Alzheimer's disease dementia often spans many years. The limited follow up duration of Leqembi's Phase II and III trials may be insufficient to conclude how effective Leqembi is for treating early Alzheimer's disease. Ultimately, longer trials are warranted to determine the true efficacy and safety of Leqembi in early Alzheimer's disease. With the lack of information surrounding long-term use, safety, and the real-world effects of Leqembi, a number of questions arise including the appropriate duration of treatment, if or at what point effectiveness will start to decline, and whether continued treatment with Leqembi is safe and necessary in patients whose amyloid beta plaque has reduced to undetectable levels.

- On April 17, 2023, ICER published its final evidence report of Leqembi for AD. ICER acknowledged that current evidence strongly suggests a Leqembi mildly slows the loss of cognition in patients with early AD; however, the risks of brain swelling and bleeding, particularly when used outside of clinical trials, did not support that average benefits of Leqembi would exceed its risks. Treatment of MCI due to Alzheimer's and mild Alzheimer's dementia with Leqembi was deemed "promising but inconclusive", and after review of the drug's clinical evidence and consideration of Leqembi's other potential benefits, disadvantages, etc., Leqembi at its current price-point represents "low" long-term value for money.

    - The report highlights that uncertainty remains around the amyloid hypothesis and that we do not have adequate data for lecanemab to show a correlation between amyloid removal and treatment effect, or differences in outcomes by achieving or not achieving amyloid negativity.

    - A substantial percentage of patients reached amyloid negativity (by PET scan) in the Phase III trial, but 7.8% of patients in the placebo arm also achieved amyloid negativity. ICER suggests that this finding demonstrates the complexity of Alzheimer's disease pathophysiology and that the role of amyloid in Alzheimer's disease and factors that may impact clinical outcomes are not fully understood.

    - ICER also makes note that the 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.

    - Additionally, there are questions of whether the trial results can be generalized to the broader mild Alzheimer's population as the average age of participants in the Phase III trial was just over 71 years of age and included participants with some comorbidities; however, two-thirds of the Alzheimer's population in the US are 75 years of age and older and likely have significant comorbidities.

    - ICER acknowledges that there is a disagreement among experts about clinical meaningfulness of the magnitude of change in the cognitive outcomes of these trials and notes that despite the demonstrated statistical significance of the reduction in cognitive decline, we cannot say with certainty that treatment with Leqembi will yield a meaningful change in the patient's status for the benefit to outweigh the risk to treatment.

- Based on the current information available, there is insufficient evidence that Leqembi provides a meaningful clinical benefit in patients with Alzheimer's disease, and that potential benefits of therapy outweigh the risks of treatment. Therefore, demonstration of a clinical benefit is warranted in on-going clinical trials.

- On July 2, 2024, the FDA approved a third anti-amyloid monoclonal antibody, Eli Lilly's Kisunla™ (donanemab-azbt), 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 joins Leqembi as the second drug in this class to gain full FDA approval based on demonstration of statistically significant clinical benefit in clinical trials. 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 safety and efficacy data from the Phase III TRAILBLAZER-ALZ-2 trial, which evaluated a similar population as Clarity AD trial, but with an additional requirement that eligible participants be grouped and analyzed based on tau levels (low/medium or high). Additionally, participants were able to discontinue therapy with Kisunla and switch to placebo if prespecified reductions in amyloid were met during the trial.

    - Patients treated with Kisunla demonstrated a statistically significant reduction in clinical decline on the integrated Alzheimer's Disease Rating Scale (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. Patients on Kisunla also demonstrated a statistically significant reduction in clinical decline on CDR-SB, the secondary endpoint, compared to placebo at week 76. 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.

    - 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.

- Shortly after Kisunla's approval, 36-month results from the open-label, long-term extension study (OLE) of Clarity AD were presented at the Alzheimer's Association International Conference 2024. The mean change from baseline in CDR-SB in the Leqembi-treated group was -0.95 after 36 months of treatment compared to a prespecified natural history cohort of Alzheimer's disease. The OLE also demonstrated a 30% reduction in the relative risk of progressing to the next disease stage. Additionally, the tau PET substudy of Clarity AD showed that with three years of continuous Leqembi treatment, 59% of patients with no or low tau accumulation at baseline showed improvement or no decline, and 51% showed improvement from baseline on the CDR-SB global cognitive and functional scale.

    - The OLE data appears 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; however, there are potential limitations to consider.

    - Not all patients in the OLE received Leqembi treatment for a full 36-months as at the end of the 18-month Clarity AD trial those on placebo were offered to switch to open-label Leqembi, and historical data based on typical Alzheimer's progression was used to conclude how these patients would respond after 36 months.

- Additionally, it should be noted that about 600 patients out of 1,800 enrolled dropped out of the 36-month study; it is unclear whether they left due to side effect concerns, issues with follow up, or due to disease progression.

- The rate of decline can also be questioned. Though the effect seems consistent with a slowing of progression by 0.45 points after 18 months and 0.95 points after 36 months , patients seem to have progressed faster in the latter 18-months of the trial than in the first. In the first 18 months, Leqembi-treated patients progressed approximately 1.2 points, but at the end of three years they progressed a total of 3.09 points.

- The Centers for Medicare & Medicaid Servies (CMS) recognizes the need for additional information surrounding treatment with Leqembi 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 provide coverage of anti-amyloid antibodies that have been granted full FDA approval 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 anti-amyloid therapies under CED requires that providers 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 population. The data being collected by these registries is expected to help answer such questions as whether Leqembi 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.

    - 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 Leqembi in combination with other anti-amyloid therapies.

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<tr><th colspan="3">Policy History</th></tr>
<tr><th>#</th><th>Date</th><th>Change Description</th></tr>
<tr><td>1.7</td><td>Effective Date: 02/13/2025</td><td>Added initial criteria, quantity limits, authorization period, and renewal criteria for Medicare benefit only</td></tr>
<tr><td>1.6</td><td>Effective Date: 08/08/2024</td><td>Supporting information updated to include 2024 Alzheimer's Association Workgroup criteria for diagnosis and staging of Alzheimer's and reference to Kisunla.</td></tr>
<tr><td>1.5</td><td>Effective Date: 12/14/2023</td><td>Supporting information updated to include additional information regarding cognitive testing, Alzheimer's disease diagnosis, and testing for the presence of amyloid. Appendix 1 added to the policy</td></tr>
<tr><td>1.4</td><td>Effective Date: 08/10/2023</td><td>Updated Medicare criteria to refer to National Coverage Determination vs. National Coverage Analysis</td></tr>
<tr><td>1.3</td><td>Effective Date: 02/02/2023</td><td>New policy - this criteria replaces previously approved preliminary criteria.</td></tr>
<tr><td>1.2</td><td>Effective Date: 01/26/2023</td><td>UM medical management system update for BCBSM and BCN
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<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>
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<tr><td>1.1</td><td>Effective Date: 01/13/2023</td><td>UM medical management system update for BCNA and MAPPO
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<tr><td>1.0</td><td>Effective Date: 12/01/2022</td><td>Preliminary drug review</td></tr>
</table>

** 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)<br><br>Fujirebio Diagnostics, Inc. | Ratio of AB 1-42 and AB 1-40 concentrations<br><br>Determines likelihood of amyloid plaques | Negative (normal): ≥ 0.073<br><br>Likely positive (abnormal): 0.059-0.072<br><br>Positive (abnormal): ≤ 0.058 | AB 1-42 accumulation leads to plaque aggregation and neurotoxicity in AD<br><br>AB 1-40 remains relatively stable and less prone to aggregating<br><br>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)<br><br>Roche | Used together to measure the ratio of pTau181 and AB 1-42 concentrations<br><br>Ratio provides a surrogate marker of amyloid plaque burden with 90% concordance with Amyloid PET imaging | Negative (normal): ratio ≤ lab-designated ratio cut-off<br><br>Positive (abnormal): ratio > lab-designated ratio cut-off | Increases in CSF pTau181 concentration is associated with more rapid cognitive decline in AD<br><br>Results below the cut-off reduces the likelihood of AD causing the cognitive impairment<br><br>Intended to be used in addition to other clinical diagnostic evaluations. |
| Elecsys beta-amyloid (1-42) CSF II and Elecsys Total-Tau CSF<br><br>Roche | Used together to measure the ratio of tTau and AB 1-42 concentrations<br><br>Ratio provides a surrogate marker of amyloid plaque burden concordant with Amyloid PET imaging | Negative (normal): ratio ≤ lab-designated ratio cut-off<br><br>Positive (abnormal): ratio > lab-designated ratio cut-off | Expected to be available 4th quarter 2023<br><br>High CSF tTau can also be found in other neurodegenerative disease (e.g., Creutzfeldt-Jakob disease)<br><br>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.