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Effective Date: 12/14/2023

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:
 - a. 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.

***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 cannot be stopped, delayed, or prevented and is a growing health crisis worldwide, affecting patients with the disease and their families. More than 12.7 million people are expected to have Alzheimer's dementia by 2050 due to the aging population.
- About 5 million individuals 65 years of age and older may have mild cognitive impairment (MCI) due to Alzheimer's disease. MCI can be the first cognitive expression of 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.
 - The American Academy of Neurology (AAN) guidelines on MCI (2018) stress the importance of appropriate diagnosis of patients presenting with MCI in order to assess for potential reversible causes of cognitive impairment and to help patients and their families understand their condition, potential outcomes, and

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planning for the future. Diagnosis is based on clinical evaluation determining cognitive function and functional status, and not solely on test scores. Conditions or risk factors contributing to MCI should be identified and treated accordingly, and medications that could contribute to cognitive impairment should be discontinued where possible.

- For patients with MCI due to Alzheimer's disease, the AAN guidelines do not recommend the use of pharmacologic therapies as no agents have demonstrated symptomatic cognitive benefit in MCI.
- 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. As with MCI, diagnosis 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.
- The lack of available disease-modifying therapies for Alzheimer's disease signifies a huge unmet need affecting millions of Americans. Current research efforts are focused on catching 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 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 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. Note that confirmation of the presence of amyloid pathology and other Alzheimer's disease biomarkers at present is not guideline recommended for the diagnosis of Alzheimer's disease at any point in the disease process. Testing for these biomarkers is primarily 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 Vizamyli™ (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.
- It should be noted that amyloid pathology can also be found in cognitively unimpaired adults and in patients with other neurodegenerative disorders; therefore, a positive amyloid PET and/or CSF result alone does not 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.
- 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.

- 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. 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.
- 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 its approval 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.
- On January 6, 2023, the FDA approved Leqembi (lecanemab-irmb) as the second humanized IgG1 monoclonal antibody directed against amyloid beta for the treatment of Alzheimer's disease. Like Aduhelm, Leqembi was approved via the accelerated approval pathway 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 testing (n=1,795). 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.

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- 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 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. 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.
- 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.

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- On April 7, 2022, the Centers for Medicare & Medicaid Services (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 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.
 - Anti-amyloid monoclonal antibodies approved based upon evidence of efficacy from a change in surrogate endpoint may be covered in a randomized controlled trial conducted under an investigational new drug (IND) application.
 - Anti-amyloid monoclonal antibodies approved based upon evidence of efficacy from a direct measure of clinical benefit may be covered in CMS-approved prospective comparative studies, for which the study data may be collected in a registry. Refer to CMS's NCD: Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease for a complete description.

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Policy History												
#	Date	Change Description										
1.5	Effective Date: 12/14/2023	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										
1.4	Effective Date: 08/10/2023	Updated Medicare criteria to refer to National Coverage Determination vs. National Coverage Analysis										
1.3	Effective Date: 02/02/2023	New policy - this criteria replaces previously approved preliminary criteria.										
1.2	Effective Date: 01/26/2023	UM medical management system update for BCBSM and BCN <table border="1" data-bbox="483 506 1365 716"> <thead> <tr> <th>Line of Business</th> <th>PA Required in Medical Management System (Yes/No)</th> </tr> </thead> <tbody> <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> </tbody> </table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	Yes	BCN	Yes	MAPPO	Yes	BCNA	Yes
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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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