Medicare Advantage Medical Benefit Drug Policy

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Effective Date: 08/10/2023

Leqembi™ (lecanemab-irmb)

HCPCS: J3590, 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. BCBSNE MA is 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:

- More than 6.5 million Americans 65 years of age 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. 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. 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, at which point 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, and eventually more severe loss of mental function and problems recognizing family and friends. 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.

- 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 planning for the future. 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.

- Historically, only symptomatic therapies have been available for treating Alzheimer's disease 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.

- MCI due to Alzheimer's disease is one of the earliest stages of the disease when symptoms start to be more visible and can be detected and diagnosed, and people with MCI due to Alzheimer's disease may exhibit biomarker evidence of changes in the brain such as abnormal levels of beta-amyloid. 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 lack of available disease-modifying therapies for Alzheimer's disease signifies a huge unmet need affecting millions of Americans.

- On June 7, 2021, the FDA approved 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.

- The accumulation of amyloid beta plaques is a defining pathophysiological feature of Alzheimer's disease, though there is insufficient evidence to definitively support that lowering beta amyloid plaque yields a clinical benefit of improved cognition and a clinically significant delay in Alzheimer's disease progression. The approval of Aduhelm not only brought a first-in-class product to market, but also the first FDA approved treatment for Alzheimer's disease that could potentially modify the disease process. Aduhelm was approved under accelerated approval based on the reduction in amyloid beta plaques observed in clinical trials, and continued approval for this indication may be contingent upon verification of a clinical benefit in an additional confirmatory trial.

- In patients with MCI due to Alzheimer's disease and mild Alzheimer's dementia, clinical trials of Aduhelm demonstrated a significant reduction in beta amyloid plaque, a biomarker historically affiliated with Alzheimer's disease and its progression. However, 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 Alzheimer's disease progression. In the time since its approval, Aduhelm has had minimal impact on the Alzheimer's patient population 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 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, 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. With 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. Testing for ApoE ε4 status is now recommended prior to initiating treatment to inform the risk of ARIA development, though it is not a requirement per the labeling.

- 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 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 in accordance with prespecified coverage criteria 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
1.2	Effective Date: 08/10/2023	Updated Medicare criteria to refer to National Coverage Determination vs. National Coverage Analysis
1.1	Effective Date: 02/02/2023	New policy - this criteria replaces previously approved preliminary criteria.
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.*