Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

Medical benefit drug policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and therefore subject to change.

Effective Date: 08/10/2023

Aduhelm™ (aducanumab-avwa)

HCPCS: J3590

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:

- 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. On July 8, 2021 the FDA updated Aduhelm's broad indication to specify that treatment should only be initiated in patients with mild forms of Alzheimer's disease 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. 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. Of note, 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, the results of which are due to the FDA by 2030.

- Aduhelm was evaluated in two pivotal Phase III randomized, double-blind, placebo-controlled, identically designed trials (EMERGE and ENGAGE; unpublished) in patients with MCI due to Alzheimer's disease or with mild Alzheimer's disease dementia who had a confirmed presence of amyloid pathology as demonstrated on amyloid PET scan or cerebrospinal fluid (CSF) amyloid lumbar puncture. Study participants were randomized to low dose Aduhelm (3 mg/kg or 6 mg/kg), high dose Aduhelm (6 mg/kg or 10 mg/kg for protocol versions 1-3; 10 mg/kg for protocol version 4 or higher), or placebo. The primary efficacy endpoint of the trials was the change from baseline at week 78 on the Clinical Dementia Rating-Sum of Boxes (CDR-SB) scale. Secondary efficacy endpoints included the change from baseline at week 78 in the following cognitive assessment scale scores: Mini Mental Status Exam (MMSE), the Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) (ADAS-Cog 13), and the Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (Mild Cognitive Impairment version) (ADCS-ADL-MCI). Both trials were terminated prior to completion due to failed preplanned futility analyses; however, an analysis of the available data yielded the following results:

- EMERGE (n = 1,638) demonstrated a statistically significant 22% reduction in clinical decline on the CDR-SB for the high-dose Aduhelm treatment arm compared to placebo at week 78 (p=0.0120). Statistically significant reductions in clinical decline as measured by the secondary endpoints were also seen in the high dose Aduhelm arm, although improvements were minimal. It should be noted that statistical significance in the change in CDR-SB may not demonstrate a clinically important change. Some experts suggest that the minimum clinically important difference in CDR-SB where a clinically meaningful change to patients, caregivers or clinicians is apparent is generally 1 to 2 on a scale of 0 to 18, and in EMERGE the absolute difference in CDR-SB was 0.39 points.

- ENGAGE (n = 1,647) despite identical trial design did not meet the primary endpoint with high dose Aduhelm which failed to demonstrate a statistically significant reduction in clinical decline on the CDR-SB compared to placebo (2% less decline, p = 0.8330). Additionally, none of the secondary endpoints were met with statistical significance.

- Biomarker substudies were conducted in subgroups of patients in each trial to evaluate the effects of Aduhelm on brain amyloid pathology as well as CSF beta amyloid and tau levels. In both EMERGE and ENGAGE, Aduhelm produced statistically significant, dose-dependent reductions in brain amyloid plaque as measured by PET at both weeks 26 and 78 compared to placebo (p>0.0001), with the magnitude of reduction larger at week 78 than week 26. Of note, biomarker evaluations were not defined endpoints in either trial and only included 30% and 35% of the study populations in EMERGE and ENGAGE, respectively.

- Due to a number of protocol amendments over the duration of the Phase III trials, not all patients in the high dose Aduhelm treatment arm were exposed to target levels of Aduhelm (i.e. 10 mg/kg). Only 29% and 22% in EMERGE and ENGAGE, respectively, received the full possible 14 doses of Aduhelm 10 mg/kg. It is unknown how or if this variation in the high dose Aduhelm arms may have affected study results.

- A Phase 1b double-blind, placebo-controlled, safety, tolerability, pharmacokinetic, and pharmacodynamic study (PRIME, n=197; unpublished) also demonstrated a statistically significant, dose dependent reduction in brain beta amyloid plaque from baseline to week 54, and exploratory endpoints of the trial found a dose-dependent slowing of progression with Aduhelm treatment based on changes from baseline in the CDR-SB and MMSE. These findings were thought to be supportive of EMERGE; however, this trial was designed to evaluate Aduhelm safety, and the clinical assessments were only exploratory as the study was not sufficiently powered to detect clinical change.

- In patients with MCI due to Alzheimer's disease and mild Alzheimer's disease dementia, clinical trials of Aduhelm have demonstrated a significant reduction in beta amyloid plaque, a biomarker historically affiliated with Alzheimer's disease and its progression. However, the discordant results of the identically designed EMERGE and ENGAGE trials have provided insufficient evidence to support that the lowering of beta amyloid plaque yields a clinical benefit of improved cognition and delayed Alzheimer's disease progression. Additionally, it is unknown whether use of Aduhelm in patients with moderate or severe Alzheimer's disease will demonstrate similar safety and efficacy as the populations evaluated in the pivotal trials.

- The cognitive decline associated with MCI and mild Alzheimer's disease dementia often spans years, and as such the 78 week follow up duration of EMERGE and ENGAGE may be insufficient to conclude how effective Aduhelm is for treating early Alzheimer's disease. At this time we have minimal information available regarding the long term use, safety, and effects of Aduhelm which brings forth a number of questions surrounding its use, including the appropriate duration of treatment, if or at what point effectiveness will start to decline, and whether continued treatment with Aduhelm is safe and necessary in patients whose amyloid beta plaque has reduced to undetectable levels. The Phase IIIb EMBARK trial is currently evaluating long-term safety, efficacy, and tolerability of Aduhelm with completion expected in 2024, and an additional FDA-mandated trial evaluating and confirming the clinical benefit of Aduhelm is not expected to have results until 2030.

- In November 2020, the FDA's Peripheral and Central Nervous System Drugs Advisory Committee overwhelmingly voted that the results from EMERGE did not provide strong evidence supporting the effectiveness of Aduhelm as a treatment for Alzheimer's disease, ultimately resulting in unanimous opposition to the approval of Aduhelm.

- On June 30, 2021 the Institute for Clinical and Economic Review (ICER) released a revised evidence report assessing the comparative clinical effectiveness and value of Aduhelm for the treatment of Alzheimer's disease. In their report, ICER concludes that evidence is insufficient to ascertain whether or not Aduhelm slows the loss of cognition in patients with Alzheimer's disease, and as such there is insufficient support that Aduhelm will provide a benefit to patients that would outweigh any potential risks and harms of treatment. The report also concludes that Aduhelm is not cost-effective based on the substantial uncertainty regarding its health benefits at its current cost of $56,000 per year (wholesale acquisition cost) for a 74 kg patient, citing that a range of $3,000 to $8,400 per year would be needed to reach standard cost-effectiveness thresholds in patients with early Alzheimer's disease.

- At a meeting convened by ICER on July 15, 2021 that included debates over the drug's cost, efficacy, and more, a committee of ICER experts unanimously voted 15 to 0 that Aduhelm does not provide benefits above routine care for Alzheimer's disease. The committee also had a majority vote that Aduhelm would have a significant negative impact on efforts to reduce health inequities.

- Based on the current information available, there is insufficient evidence that Aduhelm provides a 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 monconal 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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<tr><th>#</th><th>Date</th><th>Change Description</th></tr>
<tr><td>1.7</td><td>Effective Date: 08/10/2023</td><td>Revised Medicare criteria to refer to the National Coverage Determination (NCD) vs. the National Coverage Analysis (NCA)</td></tr>
<tr><td>1.6</td><td>Effective Date: 06/08/2023</td><td>Annual review of criteria was performed, no changes were made</td></tr>
<tr><td>1.5</td><td>Effective Date: 06/09/2022</td><td>Medicare criteria updated to allow coverage when used in accordance with CMS's National Coverage Analysis for monoclonal antibodies directed against amyloid for the treatment of Alzheimer's disease</td></tr>
<tr><td>1.4</td><td>Effective Date: 08/23/2021</td><td>UM medical management system update for BCBS
<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></td></tr>
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<tr><td>1.0</td><td>Effective Date: 12/03/2020</td><td>Preliminary drug review</td></tr>
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** 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.*