09-J4000-01

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Reviewed: 06/25/21

Revised: 01/01/22

Subject: Aducanumab-avwa (Aduhelm™)

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DESCRIPTION:

Alzheimer's disease (AD) is a gradual and progressive cognitive impairment primarily affecting adults 65 years of age and older. The prevalence of AD and associated dementias is increasing in the United States as individuals live to older ages. Current data indicates the prevalence of AD doubles every 5 years in those 65 to 85 years old, increasing from 1% to 2% at age 65, up to more than 30% by age 85. The median survival of adults diagnosed with dementia at age 60-69 years is about 6.7 years and lower in adults diagnosed at later ages. While the exact cause of AD is unknown, Alzheimer neuropathology has been found to include neurofibrillary tangles (comprised of tau protein) that build up inside the brain's nerve cells and plaques (comprised of beta-amyloid protein) that build up in the spaces between the brain's nerve cells. This pathology results in gradual impairment in cognition and memory that ultimately interferes with function and daily activities. Treatment should be guided by dementia severity and include both pharmacologic and non-pharmacologic interventions. Cholinesterase inhibitors (e.g., donepezil, rivastigmine, galantamine) and memantine are FDA approved for treatment of AD.

Aducanumab (Aduhelm), a monoclonal antibody, was approved by the U.S. Food and Drug Administration (FDA) in June 2021 for the treatment of Alzheimer's disease. This indication was approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with aducanumab and continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s). Aducanumab targets the build-up of amyloid plaque in the brain. It is administered as a monthly IV infusion. In July 2021, the FDA revised the approved indication to include the following, "Treatment with ADUHELM should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied."

The safety and efficacy of aducanumab were evaluated in subjects with mild cognitive impairment or mild AD in two identically designed phase 3, multicenter, randomized, double-blind placebo-controlled clinical trials (EMERGE, ENGAGE). Key inclusion and exclusion criteria for these trials is below:

Key Inclusion Criteria	Key Exclusion Criteria
• Must meet all of the following clinical criteria for MCI due to AD or mild AD and must have: • A Clinical Dementia Rating (CDR)-Global Score of 0.5. • Objective evidence of cognitive impairment at screening • An MMSE score between 24 and 30 (inclusive) • Must have a positive amyloid Positron Emission Tomography (PET) scan • Must consent to apolipoprotein E (ApoE) genotyping • If using drugs to treat symptoms related to AD, doses must be stable for at least 8 weeks prior to screening visit 1 • Must have a reliable informant or caregiver	• Any medical or neurological condition (other than Alzheimer's Disease) that might be a contributing cause of the subject's cognitive impairment • Have had a stroke or Transient Ischemic Attack (TIA) or unexplained loss of consciousness in the past 1 year • Clinically significant unstable psychiatric illness in past 6 months • History of unstable angina, myocardial infarction, advanced chronic heart failure, or clinically significant conduction abnormalities within 1 year prior to Screening • Indication of impaired renal or liver function • Have human immunodeficiency virus (HIV) infection • Have a significant systematic illness or infection in past 30 days • Relevant brain hemorrhage, bleeding disorder and cerebrovascular abnormalities • Any contraindications to brain magnetic resonance imaging (MRI) or PET scans • Alcohol or substance abuse in past 1 year • Taking blood thinners (except for aspirin at a prophylactic dose or less)

Participants were randomized to low-dose aducanumab, high-dose aducanumab, or placebo. The primary outcome was the change from baseline in Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) score. The CDR-SB is an assessment of cognition (three domains: memory, orientation, judgment/problem-solving) and function (three domains: community affairs, home/hobbies, personal care). Each domain is graded from 0 to 3 based on performance severity (0 = no performance disability, 3 = severe performance disability) and summed for a total score ranging from 0 to 18. Higher scores suggest greater disease severity. The minimal clinically important difference for CDR-SB is estimated to be 1-2 points. Secondary outcome measures in both trials were change from baseline in MMSE score, change from baseline in Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) (ADAS-Cog 13), and change from baseline in Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) (ADCS-ADL-MCI) score.

Due to concerns of amyloid related imaging abnormalities (ARIA) and vasogenic edema (ARIA-E) in participants receiving high-dose aducanumab who were apolipoprotein E (APOE) ε4 carriers, EMERGE and ENGAGE were initially designed to test low-dose aducanumab up to 6 mg/kg in APOE ε4 carriers. Noncarriers could titrate to 10 mg/kg. Ultimately it was recognized that ARIA and ARIA-E were reversible if immediately recognized and would not reappear if rechallenged. In March 2017, a year and a half after study enrollment began, Biogen revised the clinical trial protocols to allow all participants to be titrated to a 10 mg/kg dose. Interestingly, Biogen did not modify the timing of a protocol-specified interim analysis for futility.

In March 2019, Biogen announced that, after an interim analysis of data through December 2018, both EMERGE and ENGAGE were being halted due to discordant results in the primary outcome. A pre-specified outcome required both trials to demonstrate a beneficial response with aducanumab. There was no treatment benefit observed in either the high- or low-dose arms at week 78 in ENGAGE. EMERGE was trending positive.

In October 2019, Biogen announced that a subsequent analysis was conducted that included an additional three months of data. In this dataset, 60% of patients from EMERGE and 66% of patients from ENGAGE had the opportunity to complete the week 78 assessment. This analysis showed that aducanumab was beneficial in slowing cognitive decline in EMERGE (22% relative reduction in the CDR-SB outcome in high-dose aducanumab compared with placebo (p=0.01)). A statistically significant difference in change from baseline in CDR-SB was observed in the high-dose arm of EMERGE (difference vs. placebo -0.39 [95% CI -0.69 to -0.09]), but not the low-dose arm. While statistically significant, the change in CDR-SB score in the high-dose group was less than the 1-2-point change that has been suggested as a minimal clinically important difference. ENGAGE did not show statistically significant differences in CDR-SB scores.

This new analysis (conducted in consultation with the FDA) was submitted as part of aducanumab's application for FDA approval.

CDR-SB Results from ENGAGE and EMERGE at Week 78, ITT Population

	ENGAGE			EMERGE		
	Placebo (n=545)	Low Dose (n=547)	High Dose (n=555)	Placebo (n=548)	Low Dose (n=543)	High Dose (n=547)
Baseline CDR-SB, Mean	2.40	2.43	2.40	2.47	2.46	2.51
Adjusted Mean Change from Baseline at Week 78 (95% CI)	1.56 (1.23, 1.77)	1.38 (1.16, 1.59)	1.59 (1.37, 1.81)	1.74 (1.51, 1.96)	1.47 (1.25, 1.70)	1.35 (1.12, 1.57)
Difference vs. Placebo (95% CI)	--	-0.18 (-0.47, 0.11)	0.03 (-0.26, 0.33)	--	-0.26 (-.57, 0.04)	-0.39* (-0.69, -0.09)
% Difference vs. Placebo	--	-12%	2%	--	-15%	-22%
p-value (vs. Placebo)	--	0.2250	0.8330	--	0.0901	0.0120
*p<0.05						

The results of the EMERGE and ENGAGE, plus one safety trial, were presented in a November 2020 meeting of the FDA's Peripheral and Central Nervous System Drugs Advisory Committee. After an extensive review, the advisory committee voted on the question of whether EMERGE, independent of ENGAGE, provided "strong evidence that supports the effectiveness of aducanumab for the treatment of Alzheimer's disease" as follows: 1 yes, 8 no, and 2 uncertain. Additionally, the committee voted if it is reasonable to consider EMERGE as primary evidence of effectiveness of aducanumab for the treatment of Alzheimer's disease: 0 yes, 10 no, and 1 uncertain.

POSITION STATEMENT:

Aducanumab-avwa (Aduhelm) **does not meet the definition of medical necessity** for all indications including, but not limited to, Alzheimer's disease (AD), cognitive impairment due to AD, and AD dementia, as a clinical benefit has not been established.

Aducanumab-avwa was granted FDA approval for treatment of Alzheimer's disease in those with mild cognitive impairment or mild dementia as studied in clinical trials. This indication was approved under an accelerated approval based on a reduction in amyloid beta plaques observed in patients treated with aducanumab. The relationship between clearance of beta amyloid in the brain and clinical improvement has not been demonstrated. Use of aducanumab may result in ARIA, including bleeding into brain tissue (at least 1 death has been attributed to this).

NOTE: An FDA advisory committee determined efficacy data on aducanumab was inconclusive given the discordant results from clinical trials.

DOSAGE/ADMINISTRATION:

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FDA-approved

- Titration is required for treatment initiation.
- The recommended maintenance dosage is 10 mg/kg administered as an intravenous infusion over approximately one hour every four weeks.
- Obtain a recent (within one year) brain MRI prior to initiating treatment.
- Obtain MRIs prior to the 7th and 12th infusions. If radiographic severe ARIA-H is observed, treatment may be continued with caution only after a clinical evaluation and a follow-up MRI demonstrates radiographic stabilization (i.e., no increase in size or number of ARIA-H).

Dose Adjustments

- None

Drug Availability

- Injection:
    - 170 mg/1.7 mL (100 mg/mL) solution in a single-dose vial
    - 300 mg/3 mL (100 mg/mL) solution in a single-dose vial

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- Amyloid Related Imaging Abnormalities (ARIA): Enhanced clinical vigilance for ARIA is recommended during the first 8 doses of treatment, particularly during titration. If a patient experiences symptoms which could be suggestive of ARIA, clinical evaluation should be performed, including MRI testing if indicated.
- Hypersensitivity Reactions: Angioedema and urticaria have occurred. If a hypersensitivity reaction occurs, promptly discontinue the infusion and initiate appropriate therapy.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J0172	Injection, aducanumab-avwa, 2 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

G30.0 – G30-9	Alzheimer's disease

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: BCBSF has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 2107/22/21.

GUIDELINE UPDATE INFORMATION:

07/01/21	New Medical Coverage Guideline.
07/22/21	Revised Position Statement
01/01/22	Revision: Added HCPCS code J0172 and removed code J3590.