MEDICAL COVERAGE POLICY	
SERVICE:	**Aducanumab-avwa (Aduhelm™)**
Policy Number:	**293**
Effective Date:	**11/01/2024**
Last Review:	**08/12/2024**
Next Review:	**08/12/2025**

Important note: *Unless otherwise indicated, medical policies will apply to all lines of business. Medical necessity as defined by this policy does not ensure the benefit is covered. This medical policy does not replace existing federal or state rules and regulations for the applicable service or supply. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan documents. See the member plan specific benefit plan document for a complete description of plan benefits, exclusions, limitations, and conditions of coverage. In the event of a discrepancy, the plan document always supersedes the information in this policy.*

SERVICE: Aducanumab-avwa (Aduhelm™)

PRIOR AUTHORIZATION: Required

POLICY: Please review the plan's EOC (Evidence of Coverage) or Summary Plan Description (SPD) for details.

For Medicare plans, please refer to Medicare NCD (National Coverage Determination) 200.3 Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (AD).

For Medicaid plans, please confirm coverage as outlined in the Texas Medicaid Provider Procedures Manual | TMHP (TMPPM). Texas Mandate HB154 is applicable for Medicaid plans.

Aducanumab (Aduhelm™) for the treatment of Alzheimer disease (AD) is considered not medically necessary as a clinical benefit has not been established in published, well-designed, controlled, clinical trials.

Aducanumab (Aduhelm™) for the treatment of all other indications is considered experimental, investigational and/or unproven.

BACKGROUND:

Alzheimer disease (AD) is an irreversible and incurable neurodegenerative disorder that is characterized by progressive memory loss and cognitive decline. AD manifests as impairment in a broad spectrum of cognitive processes, typically presenting with an insidious decline in verbal and nonverbal memory, and gradually progressing to deficits in recognition, language, semantics, attention, executive function, visuoperceptual and spatial abilities, and sensory and motor skills. Memory loss is a common presenting complaint in individuals with AD. AD is the most common cause of dementia among older adults, affecting more than 5 million Americans.

The pathogenesis of AD is not yet fully understood. Autopsy findings in the brains of patients with AD reveal widespread neuropathological changes including cerebral atrophy, cellular degeneration, reactive gliosis, and neuronal and synaptic losses as well as reductions in esters and enzymes needed for successful neurotransmission. These changes are accompanied by the 2 hallmarks of AD: extracellular plaques consisting of amyloid beta peptide, and intracellular neurofibrillary tangles consisting of abnormally phosphorylated tau protein. Amyloid beta accumulation is considered to be a

hallmark of early onset of AD; it is also proposed to be an activator for aggregation of phosphorylated tau. As such, amyloid beta is predicted to be a potentially efficient target for drug/biologic therapy.

A number of genetic risk factors for AD have been proposed. The apolipoprotein E (APOE) gene is a susceptibility gene for both familial and sporadic AD. The APOE ε4 allele has been reported to increase risk by 4 times when 1 copy is present, and 12 times when 2 copies are present. It is important to note that not all individuals with ε4 alleles develop AD, thus highlighting the importance of other factors in the pathogenesis of AD.

Current medications donepezil, rivastigmine, memantine, and galantamine have limitations, as they are not effective in all patients and do not change the course of the disease. There is a need for medications that consistently produce a clinically significant effect on disease progression; aducanumab was developed to address this need.

Aducanumab (Aduhelm™) is an IgG1 human monoclonal anti-amyloid beta antibody indicated for the treatment of Alzheimer disease (AD). The rationale for the use of aducanumab is based on the hypothesis that the accumulation of amyloid beta is a main driver of AD. The deposition of amyloid beta plaques in the brain occurs before the onset of clinical symptoms and dementia. It is proposed that aducanumab may slow and potentially reverse the accumulation of amyloid beta, thus preventing or slowing disease progression.

Aducanumab evidence is limited to a single phase I/II randomized placebo-controlled ascending-dose study investigating the pharmacokinetics, safety, and tolerability of aducanumab for the treatment of mild-to-moderate AD. Eligible participants were patients aged 55 to 85 years with probable AD based on the National Institute of Neurological and Communicative Disease and Stroke and Alzheimer's Disease and Related Disorders Association criteria, dementia of Alzheimer's type as defined by the Diagnostic and Statistical Manual of Mental Disorders – Text Revision criteria, and a Mini-Mental State Examination score of 14 to 16.

The study included 53 participants with a mean age of 67.7 years (range, 55 to 84 years). Participants were randomized to receive a single dose of aducanumab 0.3 mg/kg (n=6), 1 mg/kg (n=6), 3 mg/kg (n=6), 10 mg/kg (n=6), 20 mg kg (n=6), 30 mg/kg (n=6), and 60 mg/kg (n=3) or placebo (n=14). Thirty-six percent of participants were carriers of the apolipoprotein E ε4 (APOE ε4) variant (23% heterozygote, 13% homozygote), a genetic risk factor for AD. There were higher percentages of APOE ε4 carriers in 2 treatment groups (67% in the 10 mg/kg aducanumab group and 50% in the 30 mg/kg aducanumab group) compared with 29% in the placebo group. One participant withdrew from the study.

The primary outcome was safety and tolerability. Secondary outcomes were the pharmacokinetic and pharmacodynamic profiles and aducanumab immunogenicity. The effect of aducanumab on potential plasma biomarkers and on cognition were exploratory outcomes.

Adverse events occurred in 21/39 (54%) participants who received aducanumab, of which adverse events in 10 (26%) participants were considered to be related to aducanumab. In the treatment groups, the most common adverse events occurring in more than 10% of participants were headache (n=8, 21%), diarrhea (n=5, 13%), and upper respiratory tract infection (n=4, 10%). Headache (n=2, 14%) and

diarrhea (n=1, 7%) were the most common adverse events in the placebo group. Three participants had severe amyloid related imaging abnormalities-edema/effusion (ARIA-E); all 3 had received the highest dose of aducanumab (60 mg/kg), and 2 were APOE ε4 carriers. One participant developed ARIA-E and ARIA-microhemorrhage/hemosiderin (ARIA-H). ARIA completely resolved in all 3 participants by weeks 8 to 15. There were no severe or serious adverse events in participants receiving ≤ 30 mg/kg aducanumab. There were no deaths, and no participants withdrew from the study because of adverse effects.

There was a dose-dependent increase in pharmacokinetic parameters (aducanumab Cmax, AUC0–last, and AUCinf).

None of the participants developed an anti-aducanumab immune response related to aducanumab treatment. Two participants in the 3 mg/kg group and 2 participants in the placebo group tested positive for anti-aducanumab antibodies before and after treatment (titers were within 1 or 2 dilutions from the detection limit). There was no impact on safety or on pharmacokinetic parameters.

There was no effect on changes in mean Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog 13) scores at 1 day, 3 weeks, and 24 weeks following administration of aducanumab. Furthermore, no significant changes on plasma levels of aggregated amyloid beta were observed.

At this time, the clinical benefit of aducanumab for the treatment of Alzheimer's Disease has not been established in published, peer-reviewed medical literature or in standard pharmacy compendia. Currently, there is no effective treatment for AD that prevents, halts, slows, or reverses disease. To date, no large, pivotal RCT, or set of RCTs, of an antiamyloid mAb has been completed, with a trial report published in the peer-reviewed medical literature demonstrating a clear (non-conflicting) improved health outcome (i.e., a meaningful clinical benefit in terms of slowing in the decline of cognition and function) for Medicare beneficiaries with AD. Thus, there is insufficient evidence to conclude that the use of monoclonal antibodies directed against amyloid is reasonable and necessary for the treatment of Alzheimer's disease.

The Centers for Medicare & Medicaid Services (CMS) covers Food and Drug Administration (FDA) approved monoclonal antibodies directed against amyloid for the treatment of AD when furnished in accordance with Section B under coverage with evidence development (CED) for patients who have a clinical diagnosis of mild cognitive impairment (MCI) due to AD or mild AD dementia, both with confirmed presence of amyloid beta pathology consistent with AD. The CED is a paradigm whereby Medicare covers items and services on the condition that they are furnished in the context of approved clinical studies or with the collection of additional clinical data. CMS's decision to use CED is because no trial involving any intervention, alone or combined, has yet demonstrated a meaningful improvement in health outcomes for patients treated with antiamyloid monoclonal antibodies for the treatment of AD.

CODES:

Important note: *Due to the wide range of applicable diagnosis codes and potential changes to codes, an inclusive list may not be presented, but the following codes may apply. Inclusion of a code in this section does not guarantee that it will be reimbursed, and patient must meet the criteria set forth in the policy language.*

CPT Codes:	
HCPCS Codes:	J0172 injection, aducanumab-avwa, 2 mg
ICD10 codes:	
ICD10 Not covered:	

POLICY HISTORY:

Status	Date	Action
New	07/22/2021	New policy
Reviewed	10/28/2021	Updated policy
Updated	09/22/2022	Added CMS NCD pending information
Updated	12/01/2022	Added CMS NCD information
Updated	09/28/2023	Updated Medicaid information
Updated	08/12/2024	Applied new format and layout

REFERENCES:

The following scientific references were utilized in the formulation of this medical policy. BSWHP will continue to review clinical evidence related to this policy and make modifications based upon the evolution of the published clinical evidence. Should additional scientific studies become available, and they are not included in the list, please forward the reference(s) to BSWHP so the information can be reviewed by the Medical Coverage Policy Committee (MCPC) and the Quality Improvement Committee (QIC) to determine if a modification of the policy is in order.

1. Aduhelm (aducanumab) [prescribing information]. Cambridge, MA: Biogen Inc; June 2021.
2. Alonso Vilatela, María Elisa et al. “Genetics of Alzheimer's disease.” *Archives of medical research* vol. 43,8 (2012): 622-31. doi:10.1016/j.arcmed.2012.10.017
3. Alzheimer's Association. “Home.” Alzheimer’s Disease and Dementia, 2016, www.alz.org/.
4. Bloom, George S. “Amyloid-β and tau: the trigger and bullet in Alzheimer disease pathogenesis.” *JAMA neurology* vol. 71,4 (2014): 505-8. doi:10.1001/jamaneurol.2013.5847
5. Ferrero, James et al. “First-in-human, double-blind, placebo-controlled, single-dose escalation study of aducanumab (BIIB037) in mild-to-moderate Alzheimer's disease.” *Alzheimer's & dementia (New York, N. Y.)* vol. 2,3 169-176. 20 Jun. 2016, doi:10.1016/j.trci.2016.06.002
6. Giri, Mohan et al. “Unraveling the genes implicated in Alzheimer's disease.” *Biomedical reports* vol. 7,2 (2017): 105-114. doi:10.3892/br.2017.927
7. Pasanen, Petra et al. “Genetics of dementia in a Finnish cohort.” *European journal of human genetics : EJHG* vol. 26,6 (2018): 827-837. doi:10.1038/s41431-018-0117-3
8. “Single Ascending Dose Study of BIIB037 in Participants with Alzheimer’s Disease - Full Text View - ClinicalTrials.gov.” Clinicaltrials.gov, 2011, clinicaltrials.gov/ct2/show/NCT01397539. Accessed 30 June 2019.

9. Sun, Xiaojuan et al. “β-Amyloid: the key peptide in the pathogenesis of Alzheimer's disease.” *Frontiers in pharmacology* vol. 6 221. 30 Sep. 2015, doi:10.3389/fphar.2015.00221
10. Tolar, Martin, et al. “Aducanumab, Gantenerumab, BAN2401, and ALZ-801—the First Wave of Amyloid-Targeting Drugs for Alzheimer’s Disease with Potential for near Term Approval.” *Alzheimer's Research & Therapy*, vol. 12, no. 1, 2020, doi:10.1186/s13195-020-00663-w.
11. U.S. Centers for Medicare & Medicaid Services. NCA - Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer’s Disease (CAG-00460N). www.cms.gov, https://www.cms.gov/medicare-coverage-database/view/nca.aspx?ncaid=305. Accessed 21 Sept 2022.
12. U.S. Centers for Medicare & Medicaid Services. NCD - Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (AD) (NCD 200.3). www.cms.gov, https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=375&ncdver=1. Accessed 18 Nov 2022.
13. Zamani, M et al. “Pharmacogenetic Study on the Effect of Rivastigmine on PS2 and APOE Genes in Iranian Alzheimer Patients.” *Dementia and geriatric cognitive disorders extra* vol. 1,1 (2011): 180-9. doi:10.1159/000329514

***Note**:*
Health Maintenance Organization (HMO) products are offered through Scott and White Health Plan dba Baylor Scott & White Health Plan, and Scott & White Care Plans dba Baylor Scott & White Care Plan. Insured PPO and EPO products are offered through Baylor Scott & White Insurance Company. Scott and White Health Plan dba Baylor Scott & White Health Plan serves as a third-party administrator for self-funded employer-sponsored plans. Baylor Scott & White Care Plan and Baylor Scott & White Insurance Company are wholly owned subsidiaries of Scott and White Health Plan. These companies are referred to collectively in this document as Baylor Scott & White Health Plan.

RightCare STAR Medicaid plans are offered through Scott and White Health Plan in the Central Managed Care Service Area (MRSA) and STAR and CHIP plans are offered through SHA LLC dba FirstCare Health Plans (FirstCare) in the Lubbock and West MRSAs.