



MEDICAL COVERAGE POLICY

SERVICE: Aducanumab-avwa (Aduhelm™)

Policy Number: 293

Effective Date: 12/01/2021

Last Review: 10/28/2021

Next Review Date: 10/28/2022

Important note:

Unless otherwise indicated, this policy will apply to all lines of business.

Even though this policy may indicate that a particular service or supply may be considered medically necessary and thus covered, this conclusion is not based upon the terms of your particular benefit plan. Each benefit plan contains its own specific provisions for coverage and exclusions. Not all benefits that are determined to be medically necessary will be covered benefits under the terms of your benefit plan. You need to consult the Evidence of Coverage (EOC) or Summary Plan Description (SPD) to determine if there are any exclusions or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and your plan of benefits, the provisions of your benefits plan will govern. However, applicable state mandates will take precedence with respect to fully insured plans and self-funded non-ERISA (e.g., government, school boards, church) plans. Unless otherwise specifically excluded, Federal mandates will apply to all plans. With respect to Medicare-linked plan members, this policy will apply unless there are Medicare policies that provide differing coverage rules, in which case Medicare coverage rules supersede guidelines in this policy. Medicare-linked plan policies will only apply to benefits paid for under Medicare rules, and not to any other health benefit plan benefits. CMS's Coverage Issues Manual can be found on the CMS website. Similarly, for Medicaid-linked plans, the Texas Medicaid Provider Procedures Manual (TMPPM) supersedes coverage guidelines in this policy where applicable.

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PRIOR AUTHORIZATION: Required

POLICY:

For Medicare plans, please refer to appropriate Medicare LCD (Local Coverage Determination) or NCD (National Coverage Determination). If there is no applicable LCD/NCD, use the criteria set forth below.

For Medicaid plans, please confirm coverage as outlined in the Texas Medicaid TMPPM.

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.

OVERVIEW:

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, visuospatial 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



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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 $\epsilon 4$ 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 $\epsilon 4$ 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 $\epsilon 4$ (APOE $\epsilon 4$) variant (23% heterozygote, 13% homozygote), a genetic risk factor for AD. There were higher percentages of APOE $\epsilon 4$ 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 $\epsilon 4$ carriers. One participant developed ARIA-E and ARIA-microhemorrhage/hemosiderin (ARIA-H). ARIA completely resolved in all 3 participants by weeks 8



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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 C_{max}, AUC_{0–last}, and AUC_{inf}).

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.

CODES:

Important note:

CODES: 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:	
CPT Not Covered:	
HCPCS codes:	C9399 Unclassified drugs or biologicals J3590 Unclassified biologics
ICD10 codes:	
ICD10 Not covered:	

CMS:

POLICY HISTORY:

Status	Date	Action
New	07/22/2021	New policy
Reviewed	10/28/2021	Updated policy

REFERENCES:

The following scientific references were utilized in the formulation of this medical policy. The health plan will continue to review clinical evidence related to this policy and may modify it at a later date 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 the health plan 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.arcm.2012.10.017



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- Alzheimer's Association. "Home." Alzheimer's Disease and Dementia, 2016, www.alz.org/.
- 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
- 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
- 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
- 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
- "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.
- 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
- 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.
- 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