Original Effective Date: 06/30/2021
Current Effective Date: 06/21/2023
Last P&T Approval/Version: 04/26/2023
Next Review Due By: 04/2024
Policy Number: C21305-A

ADUHELM (aducanumab-avwa) NC

PRODUCTS AFFECTED

ADUHELM (aducanumab-avwa)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.
This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Alzheimer's disease

REQUIRED MEDICAL INFORMATION:
ADUHELM (aducanumab-avwa) is considered not medically necessary for all indications, including Alzheimer's disease, due to insufficient evidence of therapeutic value since clinical benefit has not been established.
The FDA's accelerated approval pathway is based on a surrogate endpoint, which in the case of Aduhelm was the reduction of amyloid beta plaque. This type of approval is contingent upon verification of clinical benefit in a confirmatory trial. The Phase 3 ENGAGE study (ClinicalTrials.gov Identifier: NCT02477800) did not meet its primary endpoint (change from baseline in CDR-SB score at 78 weeks). Pivotal trials were not designed to evaluate long-term safety and a clinical benefit of ADUHELM (aducanumab-avwa) has not been established. The he U.S. Food and Drug Administration (FDA) Peripheral and Central Nervous System Drugs Advisory Committee said there was no conclusive evidence that Aduhelm could slow mental decline in people in the early stages of Alzheimer disease and noted that it could cause potentially serious side effects of brain swelling and brain bleeding.
Molina Healthcare will continue to evaluate and update this policy as relevant clinical evidence becomes available to determine whether ADUHELM (aducanumab-avwa) provides clear clinical benefit or slows progression of the disease.

CONTINUATION OF THERAPY:
NA

DURATION OF APPROVAL:
NA

PRESCRIBER REQUIREMENTS:
NA

AGE RESTRICTIONS:
NA

QUANTITY:
NA

PLACE OF ADMINISTRATION:
NA

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Intravenous

DRUG CLASS:
Alzheimer's Treatment - Anti-Amyloid Antibodies

FDA-APPROVED USES:
Indicated for the treatment of Alzheimer’s disease.
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. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with ADUHELM. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s)

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
An estimated 24 million people worldwide have dementia, the majority of whom are thought to have Alzheimer's disease. Thus, Alzheimer's disease represents a major public health concern and has been identified as a research priority. Although there are licensed treatments that can alleviate symptoms of Alzheimer's disease, there is a pressing need to improve our understanding of pathogenesis to enable development of disease-modifying treatments. Methods for improving diagnosis are also moving forward, but a better consensus is needed for development of a panel of biological and neuroimaging biomarkers that

support clinical diagnosis. There is now strong evidence of potential risk and protective factors for Alzheimer's disease, dementia, and cognitive decline, but further work is needed to understand these better and to establish whether interventions can substantially lower these risks. In this Seminar, we provide an overview of recent evidence regarding the epidemiology, pathogenesis, diagnosis, and treatment of Alzheimer's disease, and discuss potential ways to reduce the risk of developing the disease.

On June 7, 2021, the FDA approved Biogen's Aduhelm (aducanumab) for the treatment of Alzheimer's disease (AD). Aduhelm is the first new drug approved for AD in 18 years, and is the first drug specifically approved to slow the progression of AD. Aduhelm is a monoclonal antibody that targets the buildup of amyloid plaque in the brain and is administered as a once-monthly intravenous infusion.
The approved indication "for the treatment of Alzheimer's disease" is the broadest label the FDA could have provided. The clinical trials for the drug were conducted on much more specific patient types, those with mild cognitive impairment (MCI) or mild Alzheimer's dementia. All patients in the trials also received a PET (positron emissions tomography) scan to confirm elevated brain amyloid levels.
The FDA's approval of Aduhelm was based on results from three Phase 3 trials, EMERGE and ENGAGE, and a Phase 1b trial, PRIME. There has been significant controversy over the trial data, as EMERGE and ENGAGE have conflicting clinical results. In the EMERGE trial, patients treated with high-dose aducanumab showed less cognitive decline than patients receiving placebo.

The efficacy of ADUHELM was evaluated in two double-blind, randomized, placebo-controlled, parallel group studies (Study 1, NCT 02484547 and Study 2, NCT 02477800) in patients with Alzheimer's disease (patients with confirmed presence of amyloid pathology and mild cognitive impairment or mild dementia stage of disease, consistent with Stage 3 and Stage 4 Alzheimer's disease stratified to include 80% Stage 3 patients and 20% Stage 4 patients). The effects of ADUHELM were also supported by a double-blind, randomized, placebo-controlled, dose ranging study (Study 3, NCT 01677572) in patients with Alzheimer's disease (patients with confirmed presence of amyloid pathology and prodromal or mild dementia stage of disease, consistent with Stage 3 and Stage 4 Alzheimer's disease, with an enrolled distribution of 43% Stage 3 patients and 57% Stage 4 patients), followed by an optional, dose-blind, long-term extension period.

In Studies 1 and 2, patients were randomized to receive ADUHELM low dose (3 or 6 mg/kg for ApoE ε4 carriers and noncarriers, respectively), ADUHELM high dose (10 mg/kg), or placebo every 4 weeks for 18 months, followed by an optional, dose-blind, long-term extension period.
Both studies included an initial titration period of up to 6 months to the maximum target dose. At the beginning of the study, ApoE ε4 carriers were initially titrated up to a maximum of 6 mg/kg in the high dose group, which was later adjusted to 10 mg/kg.
In Studies 1 and 2, patients were enrolled with a Clinical Dementia Rating (CDR) global score of 0.5, a Repeatable Battery for Assessment of Neuropsychological Status (RBANS) delayed memory index score ≤ 85, and a Mini-Mental State Examination (MMSE) score of 24-30. In Study 3, patients were enrolled with a global CDR score of 0.5 or 1.0 and an MMSE score of 20-30. Patients were enrolled with or without concomitant approved therapies (cholinesterase inhibitors and the N-methyl-D-aspartate antagonist memantine) for Alzheimer's disease. Studies 1 and 2 were terminated prior to their planned completion. Study endpoints were analyzed based on the prespecified statistical analysis plan

Study 1

In Study 1, 1638 patients were randomized 1:1:1 to receive ADUHELM low dose, ADUHELM high dose, or placebo. At baseline, the mean age of patients was 71 years, with a range of 50 to 85 years. A subgroup of 488 patients were enrolled in the amyloid PET substudy; of these, 302 were evaluated at week 78.

The primary efficacy endpoint was the change from baseline on the CDR-Sum of Boxes (CDRSB) at Week 78. In Study 1, treatment with ADUHELM high dose demonstrated reduced clinical decline, as evidenced by a statistically significant treatment effect on change from baseline in CDR-SB compared to placebo (-0.39 [-22%], p = 0.0120).

Secondary efficacy endpoints included the change from baseline in MMSE score at Week 78, the change from baseline in the Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) (ADAS-Cog 13) at Week 78, and the change from baseline in the Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (Mild Cognitive Impairment version) (ADCS-ADL-MCI) score at Week 78. In Study 1, statistically significant differences from placebo were observed in the ADUHELM high dose group on all secondary efficacy endpoints evaluated. The estimate of the treatment effect favored ADUHELM across most prespecified subgroups of interest for the secondary efficacy endpoints. The Neuropsychiatric Inventory-10 item (NPI-10) was the only tertiary endpoint that assessed efficacy.

Table 4: Biomarker Results of ADUHELM in Study 1

Biomarker Endpoint at Week 78[1]	**ADUHELM High dose**	**Placebo**
Amyloid Beta PET Composite SUVR	N=170	N=159
Mean baseline	1.383	1.375
Change from baseline Difference from placebo	-0.264 -0.278, p<0.0001	0.014
Amyloid Beta PET Centiloid	N=170	N=159
Mean baseline	85.3	83.5
Change from baseline (%) Difference from placebo	-60.8 (-71%) -64.2, p<0.0001	3.4
CSF p-Tau (pg/mL)	N=17	N=28
Mean baseline	100.11	72.55
Change from baseline Difference from placebo	-22.93 -22.44, p=0.0005	-0.49
CSF t-Tau (pg/mL)	N=17	N=28
Mean baseline	686.65	484.00
Change from baseline Difference from placebo	-112.44 -112.05, p=0.0088	-0.39

[1]P-values were not statistically controlled for multiple comparisons.

Table 5: Clinical Results of ADUHELM in Study 1

Clinical Endpoint at Week 78	ADUHELM High dose (N=547)	Placebo (N=548)
CDR-SB		
Mean baseline	2.51	2.47
Change from baseline	1.35	1.74
Difference from placebo (%)	-0.39 (-22%)	
	p=0.0120	
MMSE		
Mean baseline	26.3	26.4
Change from baseline	-2.7	-3.3
Difference from placebo (%)	0.6 (-18%)	
	p=0.0493	
ADAS-Cog 13		
Mean baseline	22.246	21.867
Change from baseline	3.763	5.162
Difference from placebo (%)	-1.400 (-27%)	
	p=0.0097	
ADCS-ADL-MCI		
Mean baseline	42.5	42.6
Change from baseline	-2.5	-4.3
Difference from placebo (%)	1.7 (-40%)	
	p=0.0006	
NPI-10[1]		
Mean baseline	4.5	4.3
Change from baseline	0.2	1.5
Difference from placebo (%)	-1.3 (-87%)	
	p=0.0215	

[1]P-value was not statistically controlled for multiple comparisons.

Study 2
In Study 2, 1647 patients were randomized 1:1:1 to receive ADUHELM low dose, ADUHELM high dose, or placebo. At baseline, the mean age of patients was 71 years, with a range of 50 to 85 years. A subgroup of 585 patients were enrolled in the amyloid PET subgroup; of these, 374 were evaluated at week 78.

No statistically significant differences were observed between the ADUHELM-treated and placebo-treated patients on the primary efficacy endpoint, the change from baseline in CDR-SB score at 78 weeks

Table 6: Biomarker Results of ADUHELM in Study 2

Biomarker Endpoint at Week 78[1]	ADUHELM High dose	Placebo
Amyloid Beta PET Composite SUVR	N=183	N=204
Mean baseline	1.407	1.376
Change from baseline Difference from placebo	-0.235 -0.232, p<0.0001	-0.003
Amyloid Beta PET Centiloid	N=183	N=204
Mean baseline	90.8	83.8
Change from baseline (%) Difference from placebo	-54.0 (-59%) -53.5, p<0.0001	-0.5
CSF p-Tau (pg/mL)	N=18	N=15
Mean baseline	121.81	94.53
Change from baseline Difference from placebo	-13.19 -10.95, p=0.3019	-2.24
CSF t-Tau (pg/mL)	N=16	N=14
Mean baseline	618.50	592.57
Change from baseline Difference from placebo	-102.51 -69.25, p=0.3098	-33.26

[1]P-values were not statistically controlled for multiple comparisons.

The results of the 3 trials were previously debated in a November 2020 meeting of the FDA's Peripheral and Central Nervous System Drugs Advisory Committee, in which, of the 11 members, only 1 member voted for aducanumab (8 members voted no and 2 were uncertain).

In an op-ed published on March 30, 2021, in The Journal of the American Medical Association (JAMA), 3 members of the FDA advisory committee (Ad Comm) who reviewed aducanumab, Biogen's investigational Alzheimer's drug, reasserted their arguments for why the FDA should not approve it. https://jamanetwork.com/journals/jama/article-abstract/2778191

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
N/A	

AVAILABLE DOSAGE FORMS:
Aduhelm SOLN 170 mg/1.7 mL (100 mg/mL) single-dose vial
Aduhelm SOLN 300 mg/3 mL (100 mg/mL) single-dose vial

REFERENCES

1. Aduhelm (aducanumab) [prescribing information]. Cambridge, MA: Biogen Inc; February 2023.
2. Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Alzheimer's disease. Lancet.2011 Mar 19;377(9770):1019-31. doi: 10.1016/S0140-6736(10)61349-9. Epub 2011 Mar 1. PMID: 21371747.
3. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, Snyder PJ, Carrillo MC, Thies B, Phelps CH. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging- Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011 May;7(3):270-9. doi: 10.1016/j.jalz.2011.03.008. Epub 2011 Apr 21. PMID: 21514249; PMCID: PMC3312027.
4. O'Bryant SE, Waring SC, Cullum CM, et al. Staging dementia using Clinical Dementia Rating Scale Sum of Boxes scores: a Texas Alzheimer's Research Consortium study. Arch Neurol. 2008;65(8):1091-1095. 10. KnightADRC. CDR® Assessment Protocol. https://knightadrc.wustl.edu/cdr/PDFs/_CDRTranslationsMasterList.pdf.
5. MMSE Mini-Mental State Examination. PAR website. https://www.parinc.com/Products/Pkey/237.
6. 221AD302 Phase 3 Study of Aducanumab (BIIB037) in Early Alzheimer's Disease (EMERGE). Clinical trials.gov
7. 221AD301 Phase 3 Study of Aducanumab (BIIB037) in Early Alzheimer's Disease (ENGAGE). Clinical trials.gov

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information FDA-Approved Uses	Q2 2023
ANNUAL REVIEW COMPLETED- No coverage criteria changes with this annual review.	Q2 2022
Q2 2022 Established tracking in new format	Historical changes on file