Draft Revised Policy: Do Not Implement

Aducanumab-avwa (Aduhelm™)

IMPORTANT REMINDER

We develop Medical Policies to provide guidance to Members and Providers. This Medical Policy relates only to the services or supplies described in it. The existence of a Medical Policy is not an authorization, certification, explanation of benefits or a contract for the service (or supply) that is referenced in the Medical Policy. For a determination of the benefits that a Member is entitled to receive under his or her health plan, the Member's health plan must be reviewed. If there is a conflict between the medical policy and a health plan or government program (e.g., TennCare), the express terms of the health plan or government program will govern.

POLICY

The proposal is to add text/statements in red and to delete text/statements with strikethrough:

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication

Aduhelm is an amyloid beta-directed antibody 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).

All other indications are considered experimental/investigational and not medically necessary.

II. DOCUMENTATION

Submission of the following information is necessary to initiate the prior authorization review:

A. Initial requests:
   1. Genetic testing results documenting a mutation in amyloid precursor protein (*APP*), presenilin-1 (*PSEN1*), or presenilin-2 (*PSEN2*), if applicable.
   2. Clinical documentation to support early onset Alzheimer's disease, if applicable.
   3. Medical records (e.g., chart notes) documenting the following:
      i. Diagnosis of mild cognitive impairment due to Alzheimer's Disease or mild Alzheimer's Disease.
      ii. Baseline assessments for any of the following assessment tools:
         a. Clinical Dementia Rating-Global Score (CDR-GS)
         b. Mini-Mental Status Exam (MMSE)
         c. Montreal Cognitive Assessment (MoCA)
   4. Presence of amyloid pathology documented by either of the following:
      i. Baseline positron emission tomography (PET) scan
      ii. Lumbar puncture results
   5. Recent (within one year) brain magnetic resonance imaging (MRI) prior to initiating treatment.
   6. Current enrollment in a randomized controlled trial conducted under an investigational new drug (IND) application or National Institutes of Health (NIH)-supported trial.

B. Continuation requests (where applicable):
   1. Medical records (e.g., chart notes) documenting the most recent (less than 1 month prior to continuation request) assessment tool for any of the following:
      i. Clinical Dementia Rating-Global Score (CDR-GS)
      ii. Mini-Mental Status Exam (MMSE)
      iii. Montreal Cognitive Assessment (MoCA)
   2. Brain magnetic resonance imaging (MRI) results prior to the 5th dose (first dose of 6 mg/kg), 7th dose (first dose of 10 mg/kg), 9th dose (third dose of 10 mg/kg), and 12th dose (sixth dose of 10 mg/kg), where applicable.
   3. Continued enrollment in a randomized controlled trial conducted under an investigational new drug (IND) application or National Institutes of Health (NIH)-supported trial.

III. EXCLUSIONS

Coverage will not be provided for members with any of the following conditions:
A. Suspected neurodegenerative etiology of cognitive impairment other than Alzheimer's disease (AD), including but not limited to frontotemporal lobar degeneration (FTLD) or Lewy body disease (i.e., meeting consensus criteria for possible or probable dementia with Lewy bodies).
B. Requirement for therapeutic anticoagulation (e.g., anticoagulants, antiplatelets), except for aspirin at a prophylaxis dose or less (no more than 325mg daily).
C. History of transient ischemic attacks (TIA), stroke, or seizures within the past 12 months.
D. Bleeding disorder that is not under adequate control (including a platelet count <50,000 or international normalized ratio [INR] > 1.5).
E. Aduhelm will not be used in combination with any other amyloid beta-directed antibodies (e.g., donanemab, lecanemab).

IV. PRESCRIBER SPECIALTIES

This medication must be prescribed by or in consultation with a geriatrician, neurologist, psychiatrist, or neuropsychiatrist.

V. CRITERIA FOR INITIAL APPROVAL

Alzheimer's Disease
Authorization of 6 months may be granted for treatment of Alzheimer's disease (AD) when all of the following criteria are met:
A. Member must meet one of the following criteria:
   1. Member is 50 years of age or older
   2. If less than 50 years of age, member has a genetic mutation in amyloid precursor protein (*APP*), presenilin-1 (*PSEN1*), or presenilin-2 (*PSEN2*), or other clinical documentation to support early onset AD.
B. Member must have mild cognitive impairment due to AD or mild AD dementia.
C. Member must have objective evidence of cognitive impairment at baseline (Appendix A).
D. Member must have one of the following scores at baseline on any of the following assessment tools:
   1. Clinical Dementia Rating-Global Score (CDR-GS) of 0.5 or 1 (Appendix B).
   2. Mini-Mental Status Examination (MMSE) score of 21 - 30 (Appendix C).
   3. Montreal Cognitive Assessment (MoCA) score of greater than or equal to 16 (Appendix D).
E. Member must meet one of the following criteria:
   1. Have a positron emission tomography (PET) scan confirming the presence of amyloid pathology.
   2. Have results from a lumbar puncture confirming at least one of the following detected in cerebrospinal fluid (CSF) as determined by the lab assay:

i. Presence of elevated phosphorylated tau (P-tau) protein and/or elevated total tau (T-tau) protein, and reduced beta amyloid-42 (AB42)
ii. Low AB42/AB40 ratio
iii. Elevated P-Tau/AB42 ratio
iv. Elevated T-Tau/AB42 ratio

F. Member must have a recent brain magnetic resonance imaging (MRI) within one year prior to initiating treatment.
G. Member meets one of the following regarding apolipoprotein E ε4 (ApoE ε4) status:
1. Genotype testing for ApoE ε4 status has been performed prior to initiation of treatment to inform member of the risk of developing ARIA.
2. Genotype testing has not been performed and the prescriber has informed the member that it cannot be determined if they are ApoE ε4 homozygous and may be at higher risk for ARIA.
H. Member must currently be enrolled in a randomized controlled trial conducted under an investigational new drug (IND) application or National Institutes of Health (NIH)-supported trial.

VI. CONTINUATION OF THERAPY

Authorization of 6 months (first reauthorization after initial 6-month approval period) may be granted for members requesting continuation of therapy when all of the following criteria are met:
A. Member has met all initial authorization criteria at the time of initial approval.
B. Member has been evaluated for evidence of amyloid-related imaging abnormalities (ARIA) on MRI prior to the 5th dose (first dose of 6 mg/kg) and the 7th dose (first dose of 10 mg/kg) (Appendix E).
1. For members with radiographic evidence of ARIA-E:
i. Dosing may continue at current dose and schedule for members that meet the following criteria:
a. Member has mild ARIA-E on MRI and is asymptomatic or has mild clinical symptoms
ii. Dosing should be suspended until MRI demonstrates radiographic resolution and symptoms resolve for members that meet any of the following criteria:
a. Member has mild ARIA-E on MRI and has moderate or severe clinical symptoms
b. Member has moderate ARIA-E on MRI and is asymptomatic or has mild, moderate, or severe clinical symptoms
c. Member has severe ARIA-E on MRI and is asymptomatic or has mild, moderate, or severe clinical symptoms
2. For members with radiographic evidence of ARIA-H:
i. Dosing may continue at current dose and schedule for members that meet the following criteria:
a. Member has mild ARIA-H on MRI and is asymptomatic
ii. Dosing should be suspended until MRI demonstrates radiographic resolution or stabilization and symptoms resolve for members that meet any of the following criteria:
a. Member has mild ARIA-H on MRI and is symptomatic
b. Member has moderate ARIA-H on MRI and is asymptomatic or symptomatic
c. Member has severe ARIA-H on MRI and is asymptomatic or symptomatic
C. Member continues to be enrolled in a randomized controlled trial conducted under an investigational new drug (IND) application or National Institutes of Health (NIH)-supported trial.

Authorization of 6 months (second reauthorization) may be granted for members requesting continuation of therapy when all of the following criteria are met:
A. Member has met all initial authorization criteria at the time of initial approval.
B. Member has been evaluated for evidence of amyloid-related imaging abnormalities (ARIA) on MRI prior to the 9th dose (third dose of 10 mg/kg) and the 12th dose (sixth dose of 10 mg/kg) (Appendix E).
1. For members with radiographic evidence of ARIA-E:
i. Dosing may continue at current dose and schedule for members that meet the following criteria:
a. Member has mild ARIA-E on MRI and is asymptomatic or has mild clinical symptoms

ii. Dosing should be suspended until MRI demonstrates radiographic resolution and symptoms resolve for members that meet any of the following criteria:
   a. Member has mild ARIA-E on MRI and has moderate or severe clinical symptoms
   b. Member has moderate ARIA-E on MRI and is asymptomatic or has mild, moderate, or severe clinical symptoms
   c. Member has severe ARIA-E on MRI and is asymptomatic or has mild, moderate, or severe clinical symptoms

2. For members with radiographic evidence of ARIA-H:
   i. Dosing may continue at current dose and schedule for members that meet the following criteria:
      a. Member has mild ARIA-H on MRI and is asymptomatic
   ii. Dosing should be suspended until MRI demonstrates radiographic resolution or stabilization and symptoms resolve for members that meet any of the following criteria:
      a. Member has mild ARIA-H on MRI and is symptomatic
      b. Member has moderate ARIA-H on MRI and is asymptomatic or symptomatic
      c. Member has severe ARIA-H on MRI and is asymptomatic or symptomatic

C. Member continues to be enrolled in a randomized controlled trial conducted under an investigational new drug (IND) application or National Institutes of Health (NIH)-supported trial.

Authorization of 12 months (reauthorizations beyond initial 18 months of therapy) may be granted for members requesting continuation of therapy when all of the following criteria are met:

A. Member has met all initial authorization criteria at the time of initial approval.
B. Member meets either of the following criteria:
   1. Member has a positive clinical response as evidence by stabilization in score in any of the following measures:
      i. CDR-GS (i.e., score of 0.5 or 1)
      ii. MMSE (i.e., score of 21 – 30)
      iii. MoCA (i.e., score of greater than or equal to 16)
   2. Member continues to be enrolled in a randomized controlled trial conducted under an investigational new drug (IND) application or National Institutes of Health (NIH)-supported trial.

VII. APPENDICES

Appendix A: Summary of clinical and cognitive evaluation for MCI due to AD

- Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e., historical or observed evidence of decline over time)
- Objective evidence of impairment in one or more cognitive domains, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains)
- Preservation of independence in functional abilities
- Not demented

Appendix B: Clinical Dementia Rating (CDR) Scale

The CDR is obtained through semi-structured interviews of patients and informants with cognitive functioning rated on a 5-point scale in the following domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The score relates to the member's level of dementia:

- 0 = Normal
- 0.5 = Very Mild Dementia
- 1 = Mild Dementia
- 2 = Moderate Dementia
- 3 = Severe Dementia

Appendix C: Mini-Mental Status Exam (MMSE)
The MMSE is scored on a 30-point scale, with items that assess orientation (temporal and spatial; 10 points), memory (registration and recall; 6 points), attention/concentration (5 points), language (verbal and written, 8 points), and visuospatial function (1 point). The score relates to the member's level of dementia:

- 25 - 30 suggests normal cognition
- 20 – 24 suggests mild dementia
- 13 – 20 suggests moderate dementia
- Less than 12 suggests severe dementia

Appendix D: Montreal Cognitive Assessment (MoCA)
Per MoCA assessment, average scores for the following ranges are:

- Mild Cognitive Impairment: 19 – 25
- Mild Dementia: 11 – 21
- Normal: 26 and above

Appendix E: ARIA MRI Classification Criteria

ARIA Type	Radiographic Severity		
	Mild	Moderate	Severe
ARIA-E	FLAIR hyperintensity confined to sulcus and or cortex/subcortical white matter in one location < 5 cm	FLAIR hyperintensity 5 to 10 cm, or more than 1 site of involvement, each measuring < 10 cm	FLAIR hyperintensity measuring > 10 cm, often with significant subcortical white matter and/or sulcal involvement. One or more separate sites of involvement may be noted.
ARIA-H microhemorrhage	≤ 4 new incident microhemorrhages	5 to 9 new incident microhemorrhages	10 or more new incident microhemorrhages
ARIA-H superficial siderosis	1 focal area of superficial siderosis	2 focal areas of superficial siderosis	> 2 focal areas of superficial siderosis

APPLICABLE TENNESSEE STATE MANDATE REQUIREMENTS

BlueCross BlueShield of Tennessee's Medical Policy complies with Tennessee Code Annotated Section 56-7-2352 regarding coverage of off-label indications of Food and Drug Administration (FDA) approved drugs when the off-label use is recognized in one of the statutorily recognized standard reference compendia or in the published peer-reviewed medical literature.

ADDITIONAL INFORMATION

For appropriate chemotherapy regimens, dosage information, contraindications, precautions, warnings, and monitoring information, please refer to one of the standard reference compendia (e.g., the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) published by the National Comprehensive Cancer Network®, Drugdex Evaluations of Micromedex Solutions at Truven Health, or The American Hospital Formulary Service Drug Information).

REFERENCES

1. Aduhelm [package insert]. Cambridge, MA: Biogen; August 2023.

2. Fagan AM, Mintun MA, Mach RH, et al. Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid Abeta42 in humans. Ann Neurol. 2006;59(3):512-519.
3. Albert MS, DeKosky ST, Dickson D, et al. 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;7(3):270-279.
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. doi:10.1001/archneur.65.8.1091.
5. CDR Dementia Staging Instrument. Knight Alzheimer Disease Research Center. https://knightadrc.wustl.edu/cdr/cdr.htm. Accessed: May 1, 2024.
6. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology. 1993 Nov;43(11):2412-4.
7. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975 Nov;12(3):189-98.
8. MoCA Cognitive Assessment. https://www.mocatest.org/. Accessed: May 1, 2024.
9. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment [published correction appears in J Am Geriatr Soc. 2019 Sep;67(9):1991]. J Am Geriatr Soc. 2005;53(4):695-699.
10. Schindler SE, Gray JD, Gordon BA, et al. Cerebrospinal fluid biomarkers measured by Elecsys assays compared to amyloid imaging. *Alzheimers Dement*. 2018;14(11):1460-1469.
11. Cummings J, Salloway S. Aducanumab: Appropriate use recommendations [published online ahead of print, 2021 Jul 27]. Alzheimers Dement. 2021;10.1002/alz.12444.
12. Patrick RE, Hobbs K, Mathias L, Harper DG, Forester BP. The Limitations of Using Cognitive Cutoff Scores for Enrollment in Alzheimer Trials. Am J Geriatr Psychiatry. 2019;27(10):1153-1158.
13. National Coverage Determination (NCD) for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (AD) (200.3 – Version 1). https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=375&ncdver=1 Accessed May 1, 2024.
14. Trzepacz PT, Hochstetler H, Wang S, Walker B, Saykin AJ; Alzheimer's Disease Neuroimaging Initiative. Relationship between the Montreal Cognitive Assessment and Mini-mental State Examination for assessment of mild cognitive impairment in older adults. BMC Geriatr. 2015 Sep 7;15:107.
15. Elecsys Phospho-Tau (181P) CSF 2022-12.

EFFECTIVE DATE

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