Clinical Policy: Aducanumab-avwa (Aduhelm)

Reference Number: ERX.SPA.379
Effective Date: 06.07.21
Last Review Date: 08.21
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Aducanumab-avwa (Aduhelm™) is a monoclonal antibody targeting amyloid beta.

FDA Approved Indication(s)
Aduhelm is indicated for the treatment of Alzheimer's disease. Treatment with Aduhelm should be initiated in paints with mild cognitive impairment or mild dementia stage of the 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).

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Aduhelm is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Alzheimer's Disease (must meet all)**:**

1. Diagnosis of Alzheimer's disease (*see Appendix E*);
2. Prescribed by a neurologist or geriatric psychiatrist;
3. Age ≥ 50 years;
4. Presence of beta-amyloid plaques verified by one of the following (a or b):
   a. Positron emission tomography (PET) scan;
   b. Cerebrospinal fluid (CSF) testing;
5. Documentation of recent (within the last year) brain magnetic resonance imaging (MRI) demonstrating all of the following (a, b, and c):
   a. No localized superficial siderosis;
   b. Less than 10 brain microhemorrhages;
   c. No brain hemorrhage > 1 cm within the past year;
6. Objective evidence of cognitive impairment at screening (*see Appendix F*);
7. Clinical Dementia Rating-Global Score (CDR-GS) of 0.5;
8. Mini-Mental State Exam (MMSE) score ≥ 24;
9. Member is currently not taking any blood thinners, except aspirin ≤ 325 mg;
10. Member has not had any brain hemorrhage, bleeding disorder, or cerebrovascular abnormalities in the last 6 months;
11. All of the following causes of dementia have been ruled out:
    a. Vascular dementia;
    b. Lewy body dementia (DLB);
    c. Frontotemporal dementia (FTD);

d. Parkinson's disease dementia;

12. Dose does not exceed the following (must meet all):
    a. Infusion 1 and 2: 1 mg/kg per 4 weeks;
    b. Infusion 3 and 4: 3 mg/kg per 4 weeks;
    c. Infusion 5 and 6: 6 mg/kg per 4 weeks.

Approval duration: 6 months (6 doses of infusion only)

B. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Alzheimer's Disease (must meet all)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy as evidenced by slowed decline in cognition;
3. Prior to the 7th and 12th infusion, documentation of recent (within the last month) brain MRI showing one of the following (a or b):
    a. Less than 10 new incident microhemorrhages and less than 2 focal areas of superficial siderosis;
    b. Radiographic stabilization since baseline (i.e., no increase in size or number of ARIA-H);
4. If request is for a dose increase, new dose does not exceed 10 mg/kg once every 4 weeks.

Approval duration:

- **Members with < 7 total infusions: up to the 6th total infusion**
- **Members with < 12 total infusions but > 7 total infusions: up to the 11th total infusion**
- **Members with > 12 total infusions: 6 infusions per PA approval**

B. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration
CDR-GS: Clinical Dementia Rating – global score
CSF: cerebrospinal fluid
DLB: Lewy body dementia
FTD: frontotemporal dementia
MMSE: Mini-Mental State Exam
MRI: magnetic resonance imaging
PET: positron emission tomography

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

None reported

Appendix D: Dementia Rating Scales

- CDR-GS is useful for characterizing and tracking a patient's level of impairment/dementia:
    - 0 = normal
    - 0.5 = very mild dementia
    - 1 = mild dementia

- 2 = moderate dementia
- 3 = severe dementia

- Clinical Dementia Rating Sum of Boxes (CDR-SB) assessment is a 5-point scale used to characterize six domains of cognitive and functional performance applicable to Alzheimer disease and related dementias: Memory, Orientation, Judgment & Problem Solving, Community Affairs, Home & Hobbies, and Personal Care. The information is obtained through an interview of the patient and a reliable informant (e.g., family member). This score is useful for characterizing and tracking a patient's level of impairment/dementia.
  - 0 suggests normal
  - 0.5 to 4 suggests questionable cognitive impairment
  - 0.5 to 2.5 suggests questionable impairment
  - 3.0 to 4.0 suggests very mild dementia
  - 4.5 to 9.0 suggests mild dementia
  - 9.5 to 15.5 suggests moderate dementia
  - 16.0 to 18.0 suggests severe dementia
- MMSE is a series of questions asked by a health professional designed to test a range of everyday mental skills. The maximum score is 30 points where the following levels of dementia are indicated and a score of:
  - 25 to 30 suggest normal cognition,
  - 20 to 24 suggests mild dementia,
  - 13 to 20 suggests moderate dementia, and
  - less than 12 indicates severe dementia.
  - On average, the MMSE score of a person with Alzheimer's declines about two to four points each year.
- The Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog 13) is the standard cognitive scale used to measure neuropsychological changes in Alzheimer's disease clinical trials. A 4-point change is generally considered as indicating a clinically meaningful difference.

Appendix E: Diagnosis of Alzheimer's disease

- Alzheimer's disease
  - Interference with ability to function at work or at usual activities
  - A decline from a previous level of functioning and performing
  - Not explained by delirium or major psychiatric disorder
  - Cognitive impairment established by history-taking from the patient and a knowledgeable informant; and objective bedside mental status examination or neuropsychological testing
  - Cognitive impairment involves a minimum of two of the following domains:
    - Impaired ability to acquire and remember new information
    - Impaired reasoning and handling of complex tasks, poor judgment
    - Impaired visuospatial abilities
    - Impaired language functions (speaking, reading, writing)
    - Changes in personality, behavior, or comportment
  - Insidious onset (gradual onset over months to years, not over hours to days)
  - Clear-cut history of worsening
  - Initial and most prominent cognitive deficits are one of the following:
    - Amnestic presentation (impairment in learning and recall of recently learned information)
    - Nonamnestic presentation in either a language presentation (prominently word-finding deficits), a visuospatial presentation with visual deficits, or executive dysfunction (prominently impaired reasoning, judgment and/or problem solving)
  - No evidence of substantial concomitant cerebrovascular disease, core features of dementia with DLB, prominent features of behavioral variant FTD or prominent features of semantic or nonfluent/agrammatic variants of primary progressive aphasia (PPA), or evidence of another concurrent, active neurologic or non-neurologic disease or use of medication that could have a substantial effect on cognition

- Mild cognitive impairment due to Alzheimer's disease – core clinical criteria
  - Concern regarding change in cognition obtained from the patient, from an informant who knows the patient well, or from a skilled clinician observing the patient
  - Objective evidence of impairment in one or more cognitive domains that is not explained by age or education
  - Preservation of independence in functional abilities
  - Not demented

Appendix F: Objective Evidence of Cognitive Impairment

- Cognitive impairment is established by history-taking from the patient and a knowledgeable informant, along with validated cognitive assessment instruments:
  - Evidence of memory impairment
  - Evidence of impairment in one or more cognitive domains that is not explained by age or education
  - Evidence of language presentation, with prominent word-finding deficits; a visuospatial presentation, with visual cognitive deficits; or a dysexecutive presentation, with prominent impairment of reasoning, judgment, and/or problem solving
  - AD Assessment Scale-Cognitive Subscale (13 items) [ADAS-Cog 13]
  - AD Cooperative Study-Activities of Daily Living Inventory (Mild Cognitive Impairment version) [ADCS-ADL-MCI]

V. Dosage and Administration

<table>
<tr><th>Indication</th><th>Dosing Regimen</th><th>Maximum Dose</th></tr>
<tr><td>Alzheimer's disease</td><td>Initial dose should be titrated up as shown below:
<table>
<tr><th>IV infusion (every 4 weeks)</th><th>Aduhelm dosage (administered over approximately one hour)</th></tr>
<tr><td>Infusion 1 and 2</td><td>1 mg/kg</td></tr>
<tr><td>Infusion 3 and 4</td><td>3 mg/kg</td></tr>
<tr><td>Infusion 5 and 6</td><td>6 mg/kg</td></tr>
<tr><td>Infusion 7 and beyond</td><td>10 mg/kg</td></tr>
</table>
After an initial titration, the recommended maintenance dose is 10 mg/kg intravenously via a 0.2 or 0.22 micron in-line filer over approximately one hour every four weeks, and at least 21 days apart.</td><td>10 mg/kg every 21 days</td></tr>
</table>

VI. Product Availability

Vial for injection (single-dose): 170 mg/1.7 mL, 300 mg/3 mL

VII. References

1. Aduhelm Prescribing Information. Cambridge, MA: Biogen, Inc.; July 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s000lbl.pdf. Accessed July 12, 2021.
2. ClinicalTrials.gov. 221AD301 Phase 3 Study of Aducanumab (BIIB037) in Early Alzheimer's Disease (ENGAGE). Available at: https://clinicaltrials.gov/ct2/show/NCT02477800. Accessed June 10, 2021.
3. ClinicalTrials.gov. 221AD302 Phase 3 Study of Aducanumab (BIIB037) in Early Alzheimer's Disease (EMERGE). Last updated May 6, 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT02484547. Accessed June 10, 2021.
4. 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.

5. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia 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):263-269.
6. Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee Meeting. Combined FDA and Applicant PCNS Drugs Advisory Committee Briefing Document. November 6, 2020. Available at: https://www.fda.gov/advisory-committees/advisory-committee-calendar/november-6-2020-meeting-peripheral-and-central-nervous-system-drugs-advisory-committee-meeting#event-materials. Accessed June 10, 2021.
7. Institute for Clinical and Economic Review: Draft Evidence Report - Aducanumab for Alzheimer's disease: Effectiveness and Value. May 5, 2021. Available at: https://icer.org/wp-content/uploads/2020/10/ICER_ALZ_Draft_Evidence_Report_050521.pdf. Accessed June 10, 2021.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created pre-emptively.	04.14.20	05.20
Modified prescriber restriction to remove "in consultation with" and specify "geriatric" psychiatrist.	11.03.20	02.21
2Q 2021 annual review: added requirement for beta-amyloid plaque verification via diagnostic method as aducanumab has only shown efficacy in patients diagnosed with beta amyloid plaques; references reviewed and updated.	02.16.21	05.21
RT1: drug is now FDA-approved – criteria updated per FDA labeling; added MRI requirements prior to initial, 7th, and 12th doses, added initial titration dosing requirement; divided continued therapy approval durations to allow verification of MRI scans prior to the 7th and 12 doses, increased the minimum age to 50 years old, added exclusion criteria related to current use of blood thinners or recent brain hemorrhage, bleeding disorder, and cerebrovascular abnormalities in the last 6 months; references reviewed and updated.	06.22.21	08.21

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.