Clinical Policy: Aducanumab-avwa (Aduhelm)

Reference Number: ERX.SPA.379
Effective Date: 06.07.21
Last Review Date: 05.22
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 **not medically necessary** for its FDA-approved indication:

I. Aduhelm is not medically necessary for the treatment of Alzheimer's disease in patients with mild cognitive impairment or mild dementia stage of the disease for the following reasons:

A. Aduhelm does not have proven efficacy in the treatment of Alzheimer's disease.

1. Phase 3 clinical trials have shown discordant results. In its second phase 3 study (Study 2), no statistically significant differences were observed between the Aduhelm-treated arm and the placebo arm on the primary efficacy endpoint of change from baseline in the clinical dementia rating scale-sum of boxes (CDR-SB) score at Week 78.
2. Phase 3 studies were terminated due to a declaration of futility. Both Study 1 and Study 2 were terminated in March 2019 following an interim analysis by independent monitors, which concluded that the drug was unlikely to benefit patients.
3. Post-hoc analysis results do not show clinically meaningful results. The analysis showed a small treatment difference of 0.39 points in CDR-SB and 0.6 points in the mini-mental state exam (MMSE), which is not considered clinically meaningful. Furthermore, post-hoc analyses are not appropriate for concluding causality of benefit.
4. The Centers of Medicare and Medicaid Services (CMS) National Coverage Analysis for Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease concluded that current evidence is insufficient to determine that use of Aduhelm is reasonable and necessary for the treatment of Alzheimer's disease. CMS still recognizes the importance and current unmet need for a safe and effective treatment for Alzheimer's disease, and has proposed Coverage with Evidence Development, allowing Medicare coverage in either CMS-approved randomized controlled trials or trials supported by the National Institute of Health.

B. Aduhelm does not have proven safety in the treatment of Alzheimer's disease.
1. In the clinical trials, a significantly higher number of amyloid-related imaging abnormality related to edema/effusion, microhemorrhages, hemosiderin deposits, and superficial siderosis of the central nervous system was observed in the treatment arm compared to the placebo arm. There is insufficient evidence to support that clinical benefits outweigh these potential harms of Aduhelm treatment.

II. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CDR-SB: clinical dementia rating scale-sum of boxes
CMS: Centers of Medicare and Medicaid Services
FDA: Food and Drug Administration
MMSE: mini-mental state exam

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

None reported

III. 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>

IV. Product Availability

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

V. 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 February 16, 2022.
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 February 16, 2022.
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 February 16, 2022.
4. 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 February 16, 2022.

5. Institute for Clinical and Economic Review: Final Evidence Report and Meeting Summary - Aducanumab for Alzheimer's disease: Effectiveness and Value. August 5, 2021. Available at: https://icer.org/wp-content/uploads/2020/10/ICER_ALZ_Final_Report_080521.pdf. Accessed February 16, 2022.

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
Revised policy to state that Aduhelm is not medically necessary based on current available evidence.	01.26.22	05.22

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.