Drug Monograph

Drug Name: **Aduhelm™ (aducanumab) vial**
Drug Class: **Anti-Alzheimer's Disease Agent, Monoclonal Antibody Targeting Amyloid Beta**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Aduhelm is available in vials of a 170 mg/1.7 ml solution and 300 mg/3 ml solution.
Manufacturer:	Distributed by: Biogen Inc., Cambridge, MA 02142.
Summary of Findings:	The efficacy of Aduhelm was evaluated in two double-blind, randomized, placebo-controlled, parallel group trials in patients suffering from Alzheimer's disease (AD). Patients were randomized in a 1:1:1 fashion to receive either low dose Aduhelm, high dose Aduhelm or placebo. The primary efficacy endpoint was the change from baseline on the Clinical Dementia Rating-Sum of Boxes (CDR-SB) at week 78. Results from the EMERGE trial showed a statistically significant treatment effect on change from baseline in CDR-SB in the high dose Aduhelm group vs placebo only (p = 0.0120). The ENGAGE trial did not show any statistically significant treatment effect at week 78 in high dose or low dose Aduhelm treated groups versus placebo.
Status Recommendation:	☒ Clinical Edit ☐ PA Required ☐ Open Access ☐ PDL
Type of PA Criteria:	☒ Appropriate Indications ☐ Non-Preferred ☐ No PA Required ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [4]

Alzheimer's disease is a degenerative brain disease that affects memory, thinking and behavior. Affecting roughly 6.2 million Americans aged 65 and older, Alzheimer's is the most common cause of dementia- accounting for about 60-80% of dementia cases. Alzheimer's disease, while still not fully understood, is believed to be the result of beta-amyloid plaque formation outside neurons and neurofibrillary, or tau tangle (protein tau) accumulation inside neurons. This beta-amyloid accumulation contributes to the damage and ultimate death of neurons by interfering with neuronal communication at the synapses while tau tangles block the transportation of nutrients and various other chemical processes essential for normal cell function and survival. Early stages of Alzheimer's disease typically affect parts of the brain key to memory. As the disease progresses, language, reasoning and social behavior are affected. In the later stages individuals lose their ability to live and function independently, which eventually leads to their demise.

Dosage Form [1]

Aduhelm is available in both 170 mg/1.7 ml solution in a single-dose vial and 300 mg/3 ml solution in a single-dose vial.

Manufacturer [1]

Distributed by: Biogen Inc., Cambridge, MA 02142.

Indication(s) [1]

Aduhelm is indicated for the treatment of Alzheimer's disease in patients with mild cognitive impairment (MCI) or dementia only.

Clinical Efficacy [1,2]

Aduhelm is a human immunoglobulin gamma 1 (IgG1) monoclonal antibody that targets aggregated soluble and insoluble forms of amyloid beta. Aduhelm works by selectively binding, with high affinity and specificity to beta amyloid protein such as amyloid beta fibrils and soluble oligomers within the brain, thus reducing formation and accumulation of plaque.

Pharmacokinetics:

Absorption	Administered Intravenously thru IV infusion
Volume of Distribution	9.63 L at steady state
Metabolism	Degradation into small peptides and amino acids via catabolic pathways
Excretion	No data available
Half-life	$t_{1/2}$=24.8 days

Clinical Trials Experience:

STUDY 1 DESIGN (EMERGE, NCT02484547)	Phase III randomized, double-blind, multicenter, placebo-controlled, parallel-group (N=1638)
INCLUSION CRITERIA	• Male or female adults 50 to 85 years old • Meet all clinical criteria for MCI due to AD or mild AD • Clinical Dementia Rating (CDR) Global Score of 0.5 • Objective evidence of cognitive impairment at screening • MMSE score between 24 and 30 inclusive • Positive amyloid Positron Emission Tomography (PET) scan • Must consent to apolipoprotein E (ApoE) genotyping • If taking medication to treat symptoms related to AD, doses must be stable for at least 8 weeks prior to screening visit 1 • Must have a reliable informant or caregiver
EXCLUSION CRITERIA	• Any medical or neurological condition (other than Alzheimer's Disease) that may be a contributing cause to cognitive impairment • Stroke or Transient Ischemic Attack (TIA) or unexplained loss of consciousness in the past 1 year • Clinically significant unstable psychiatric illness in the past 6 months • History of unstable angina, myocardial infarction, advanced chronic heart failure, or clinically significant conduction abnormalities within 1 year prior to screening • Indication of impaired renal or liver function • HIV infection • Significant systemic illness or infection in past 30 days • Relevant brain hemorrhage, bleeding disorder and cerebrovascular abnormalities • Any contraindications to brain magnetic resonance imaging (MRI) or PET scans • Alcohol or substance abuse in past 1 year • Taking blood thinners (except aspirin at prophylactic dose or less)

TREATMENT REGIMEN	• Randomized 1:1:1
	  ○ Aduhelm low dose (3 or 6 mg/kg for ApoE 4 carriers and non-carriers respectively)
	  ○ Aduhelm high dose (10 mg/kg)
	  ○ Placebo
	• Patients received treatment every 4 weeks for 18 months followed by an optional, dose-blind, long-term extension period.

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- All participants underwent an initial titration period of up to 6 months to the maximum target dose. ApoE 4 carriers were initially titrated up to a maximum of 6 mg/kg in the high dose group and later adjusted to the 10 mg/kg dose.

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<tr><td>RESULTS</td><td>

- Primary efficacy endpoint was the change from baseline in CDR-SB score at week 78.
  - High dose Aduhelm showed statistically significant treatment effect on change from baseline in CDR-SB vs. placebo (-0.39 [-22%], p = 0.0120).

** Low dose Aduhelm showed no statistical significance in treatment vs. placebo.

- Secondary efficacy endpoints:
  - Change from baseline in MMSE score, Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) (ADAS-Cog 13), and Alzheimer's Disease Cooperative Study- Activities of Daily Living Inventory (Mild Cognitive Impairment version) (ADCS-ADL-MCI) score at week 78

** Statistically significant differences from placebo were observed in the high dose Aduhelm group on all secondary efficacy endpoints.

<table>
<tr><th>Clinical Endpoint at Week 78</th><th>Aduhelm High dose (N=547)</th><th>Placebo (N=548)</th></tr>
<tr><td>MMSE
Mean baseline</td><td>26.3</td><td>26.4</td></tr>
<tr><td>Change from baseline
Difference from placebo (%)</td><td>-2.7
0.6 (-18%)
p = 0.0493</td><td>-3.3</td></tr>
<tr><td>ADAS-Cog 13
Mean baseline</td><td>22.246</td><td>21.867</td></tr>
<tr><td>Change from baseline
Difference from placebo (%)</td><td>3.763
-1.400 (-27%)
p = 0.0097</td><td>5.162</td></tr>
<tr><td>ADCS-ADL-MCI
Mean baseline</td><td>42.5</td><td>42.6</td></tr>
<tr><td>Change from baseline
Difference from placebo (%)</td><td>-2.5
1.7 (-40%)
p = 0.0006</td><td>-4.3</td></tr>
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<tr><td>SAFETY</td><td>Discussed in the Adverse Effects section below.</td></tr>
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Clinical Trials Experience:

STUDY 2 DESIGN (ENGAGE, NCT02477800)	Phase III randomized, double-blind, multicenter, placebo-controlled, parallel-group (N=1647)
INCLUSION CRITERIA	• Male or Female adults 50 to 85 years old • Meet all clinical criteria for MCI due to AD or mild AD • Clinical Dementia Rating (CDR) Global Score of 0.5 • Objective evidence of cognitive impairment at screening • MMSE score between 24 and 30 inclusive • Positive amyloid Positron Emission Tomography (PET) scan • Must consent to apolipoprotein E (ApoE) genotyping • If taking medication to treat symptoms related to AD, doses must be stable for at least 8 weeks prior to screening visit 1 • Must have a reliable informant or caregiver
EXCLUSION CRITERIA	• Any medical or neurological condition (other than Alzheimer's Disease) that may be a contributing cause to cognitive impairment • Stroke or Transient Ischemic Attack (TIA) or unexplained loss of consciousness in the past 1 year • Clinically significant unstable psychiatric illness in the past 6 months • History of unstable angina, myocardial infarction, advanced chronic heart failure, or clinically significant conduction abnormalities within 1 year prior to screening • Indication of impaired renal or liver function • HIV infection • Significant systemic illness or infection in past 30 days • Relevant brain hemorrhage, bleeding disorder and cerebrovascular abnormalities • Any contraindications to brain magnetic resonance imaging (MRI) or PET scans • Alcohol or substance abuse in past 1 year • Taking blood thinners (except aspirin at prophylactic dose or less)
TREATMENT REGIMEN	• Randomized 1:1:1 o Aduhelm low dose (3 or 6 mg/kg for ApoE 4 carriers and non-carriers respectively) o Aduhelm high dose (10 mg/kg) o Placebo ● Patients received treatment every 4 weeks for 18 months followed by an optional, dose-blind, long-term extension period. ● All participants underwent an initial titration period of up to 6 months to the maximum target dose. ApoE 4 carriers were initially titrated up to a maximum of 6 mg/kg in the high dose group and later adjusted to the 10 mg/kg dose.
RESULTS	● No statistically significant differences were observed between the Aduhelm treated vs. placebo treated patients in primary efficacy endpoint: change from baseline in CDR-SB score at 78 weeks. **Biomarker Results of Aduhelm** **Biomarker Endpoint at Week 78*** | |

		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
	*(P-values were not statistically controlled for multiple comparisons)		
SAFETY	Discussed in the Adverse Effects section below.		

Contraindications (1)

- Hypersensitivity to Aducanumab or any of the inactive ingredients

Warnings and Precautions (1)

- Use with caution in patients with known hamster protein hypersensitivity
- May cause amyloid-related imaging abnormalities-edema (ARIA-E)
- May cause amyloid-related imaging abnormalities-hemosiderin deposition (ARIA-H)
- Pregnancy data is lacking; weigh potential risk vs. benefit

Adverse Effects (1)

Most common, ≥ 8 %	Aduhelm	

	10 mg/kg (N=1105) %	Placebo (N=1087) %
ARIA-E	35	3
Headache	21	16
ARIA-H microhemorrhage	19	7
ARIA-H superficial siderosis	15	2
Fall	15	12
Diarrhea	9	7
Confusion	8	4

Drug Interactions [(1)]

- There are no known drug interactions associated with Aducanumab.

Dosage and Administration [(1,2)]

Maintenance dose:

- 10 mg/kg IV infusion over 60 minutes given every 4 weeks (at least 21 days apart) after completing titration schedule.**
- Titration schedule: Given every 4 weeks and administered over 60 minutes
  - Infusion 1 and 2: 1 mg/kg IV infusion
  - Infusion 3 and 4: 3 mg/kg IV infusion
  - Infusion 5 and 6: 6 mg/kg IV infusion
  - Infusion 7 and beyond: 10 mg/kg IV infusion
- Preparation:
  - Utilizing aseptic technique, further dilution is required prior to administration.
  - Each vial is for single-use only and contains no preservative (Discard any unused portion)
  - Withdraw the required volume of aducanumab from the vial(s) and add to an infusion bag of 100 mL of 0.9% Sodium Chloride Injection. ** *No other diluent is to be used for preparation.*
  - Mix the aducanumab diluted solution by gentle inversion; do not shake.
- Storage:
  - After dilution, immediate use is recommended.
  - If not able to administer immediately, diluted solution may be stored in the refrigerator at 2 to 8 degrees C (36 to 46 degrees F) for up to 3 days or at room temperature up to 30 degrees C (86 degrees F) for up to 12 hours.
- Administration:
  - Prior to infusion, allow the mixed solution to warm to room temperature if kept in the refrigerator. Inspect the solution for any discoloration, or foreign particles.
  - Infuse diluted solution intravenously over approximately 1 hour through a dedicated IV line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter.

Cost [(3)]

Generic Name	Brand Name	Manufacturer	Dose	Cost**/ Year

Aducanumab	Aduhelm™	Biogen Inc.	10 mg/kg IV every 4 weeks after a 28 week titration period	$56,000 (Based on average patient's weight being 74 kg)

** Wholesale Acquisition Cost

Conclusion

Aduhelm is the first FDA-approved recombinant human immunoglobulin gamma 1 (IgG1) monoclonal antibody indicated for the treatment of Alzheimer's disease. Aduhelm was approved on an accelerated basis due to the reduction in amyloid beta plaque observed in patients treated with Aduhelm. Two trials, EMERGE and ENGAGE showed conflicting data on the primary efficacy endpoint of Aduhelm use, leaving questions about the true benefit of its use. Continued approval will be contingent upon verification of clinical benefit in confirmatory trials mandated by the FDA.

Recommendation

The MO Healthnet Division recommends adding this drug to a new Aduhelm clinical edit.

References

1) Aduhelm (aducanumab) package insert. Cambridge, MA: Biogen Inc; 2021 June.
2) Clinical Pharmacology [Accessed 2021 August]. Available at URL: https://www.clinicalkey.com/pharmacology/.
3) IPD Analytics. CNS: Alzheimer's. Accessed August 5, 2021. Available at URL: https://secure.ipdanalytics.com/User/Pharma/RxStrategy/Page/bfe5ccb0-8893-4ca0-9400-3996b1a87ab7#section-group-211845
4) "2021 Alzheimer's Disease Facts and Figures: At a Glance." *Alzheimer's Association.org.,* 2021 March 2. URL. https://www.alz.org/news/2021/new-alzheimers-association-report-examines-racial Accessed 05 August 2021.

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