Anti-amyloid-β monoclonal antibodies:

aducanumab-avwa (Aduhelm®; lecanemab-irmb (Leqembi™)

Date of Origin: 06/23/2021 **Last Review Date: 02/22/2023** **Effective Date: 02/22/2023**

Dates Reviewed: 06/23/2021, 07/28/2021, 02/22/2023

Developed By: Medical Criteria Committee

I. Length of Authorization

N/A

II. Dosing Limits

N/A

III. Initial Approval Criteria

Aducanumab (Aduhelm) and lecanemab (Leqembi) are considered **Experimental or Investigational** for the treatment of Alzheimer's disease as defined by a treatment for which scientific or medical assessment has not been completed, or the effectiveness of the treatment has not been generally established. For more information, please reference the member handbook.

IV. Renewal Criteria

N/A

V. Supporting Evidence

I. Aducanumab (Aduhelm) and lecanemab (Leqembi) are indicated for the treatment of Alzheimer's disease in patients with mild cognitive impairment or mild dementia stage of the disease. They are monoclonal antibodies that target the buildup of amyloid plaque in the brain and are administered once or twice monthly as an intravenous infusion.

II. This indication is approved under the accelerated approval pathway based on a reduction in amyloid beta plaques observed in patients treated with aducanumab (Aduhelm) or lecanemab (Leqembi). Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.

III. In November 2020 an independent panel of experts advising the FDA evaluated the data and argued that the benefit of aducanumab (Aduhelm) did not outweigh the risks. Ten of the eleven panelists voted that the presented data could not be considered as evidence of effectiveness, while the remaining panelist was uncertain. Although the FDA does not have to take the recommendation of the Advisory Committee,

it generally does. The FDA did not hold an advisory committee meeting for lecanemab (Leqembi), which was granted priority review.

IV. Originally the FDA broadly approved the use of aducanumab (Aduhelm) for "the treatment of Alzheimer's disease." However, the clinical studies in the development program included a more specific patient population who had mild cognitive impairment (MCI) or mild Alzheimer's disease. About a month after approval, the FDA revised the indication to specifically address the patient population studied, which included those with MCI or mild dementia. Patients in the clinical studies also had confirmation of elevated brain amyloid levels via positron emissions tomography (PET) scan.

V. MCI is defined as the "symptomatic pre-dementia stage" on the continuum of cognitive decline and is characterized by objective impairment in cognition that is not severe enough to require help with usual activities of daily living. MCI is considered when there is concern regarding a change in cognition from the patient, caregiver, or clinician, objective evidence of impairment based on cognitive testing (e.g. memory, executive function, attention, language), and when there is preservation of independence in functional abilities and no evidence of significant impairment in social or occupational functioning.

VI. Clinical characteristics suggestive that MCI is due to Alzheimer's disease include the following:
    a. Memory impairment is present
    b. Progressive decline in cognition over months to years
    c. Lack of Parkinsonism and visual hallucinations
    d. Lack of vascular risk factors and extensive cerebrovascular disease on brain imaging
    e. Lack of prominent behavioral or language disorders

VII. **Aducanumab (Aduhelm) clinical development:**
    a. Aducanumab (Aduhelm) was studied in two identically designed phase 3 trials (ENGAGE and EMERGE) which included a total of 3,285 patients with either MCI due to Alzheimer's disease of mild Alzheimer's disease dementia. An additional dose-ranging study, PRIME, was also used to support FDA approval. All patients included in the ENGAGE and EMERGE clinical studies met the following baseline parameters for select cognitive function testing:
        i. Clinical Dementia Rating (CDR) global score of 0.5; and
        ii. Repeatable Battery for Assessment of Neuropsychological Status (RBANS) delayed memory index score ≤ 85; and
        iii. Mini-Mental State Examination (MMSE) score of 24-30 were included in the study.

    Further, all patients had objective evidence of cognitive impairment at screening. All patients also had amyloid pathology confirmed via PET scan. The age range of patients included in the clinical studies was 50-85 years. Further, patients were excluded from the trial if they had any medical or neurological condition (other than Alzheimer's disease) that might be a contributing cause to the cognitive impairment, or brain hemorrhage, bleeding disorder, or cerebrovascular abnormalities.
    b. Despite the identical trial design of ENGAGE and EMERGE, the results between the two studies were inconsistent. Both studies were terminated in March 2019 following a prespecified interim analysis that predicted that the trials would not meet their primary endpoints. Later, after reviewing the data further, it was announced that the prior analysis of EMERGE was incorrect and it had met its primary endpoint for a subset of patients, while ENGAGE did not. Results reported

are analyzed based on the prespecified statistical analysis plan.

i. Primary Endpoint: The primary efficacy endpoint was the change from baseline on the CDR-Sum or Boxes (CDR-SB) following 78 weeks of treatment.
    1. In the EMERGE study there was a statistically significant difference in change from baseline in CDR-SB in the high-dose treatment group compared to placebo (difference vs placebo -0.39 [95% CI -0.69 to -0.09]). Differences from placebo in the aducanumab (Aduhelm) low-dose group showed a numerical difference but were not statistically significant. The change in CDR-SB score in the high-dose group was less than the 1- to 2-point change that has been suggested as a minimal clinically important difference.
    2. In the ENGAGE study, no statistically significant difference was observed in the change from baseline in CDR-SB score following 78 weeks of treatment between the aducanumab (Aduhelm) and placebo groups.

ii. Secondary Endpoint(s): Secondary efficacy endpoints included the change from baseline in MMSE score, change from baseline in the Alzheimer's Disease Assessment Scale-Cognitive Subscale (13 items) (ADAS-Cog 13), and change from baseline in the Alzheimer's disease Cooperative Study – Activities of Daily Living Inventory (Mild Cognitive Impairment version) (ADCS-ADL-MCI) score following 78 weeks of treatment.

iii. In the EMERGE study, statistically significant differences from placebo were observed in the high dose aducanumab (Aduhelm) group on all secondary endpoints evaluated.

iv. Secondary outcome results were not reported for the ENGAGE study.

c. Multiple hypotheses have tried to explain the conflicting clinical trial results, but these remain exploratory at this time given that they were done post-hoc.

d. The safety of aducanumab (Aduhelm) was evaluated in 3,078 patients who received at least one dose of the medication. Pooled safety data show that 90.7% of patients receiving aducanumab (Aduhelm) vs 86.9% of placebo-treated patients experienced an adverse event (AE). The most common AEs included amyloid-related imaging abnormalities (ARIA), headache, falls, and diarrhea. One patient in the aducanumab (Aduhelm) arm of an earlier phase trial died of an intracranial hemorrhage determined to be related to the study treatment.

e. ARIAs are a common, dose-dependent effect of amyloid-targeting antibodies and can be divided into ARIA due to edema/effusion (ARIA-E) or bran microhemorrhage or localized superficial siderosis (ARIA-H). Given the mechanism of action, this was an AE of special interest. In the clinical trials titration over 24 weeks, baseline and follow-up MRIs, and dose suspensions were utilized to minimize the risk.

f. ARIA was common in the treatment groups, with over one-third of patients experiencing this adverse event. In the high-dose arm of ENGAGE and EMERGE, 41.3% of participants experienced ARIA compared to 10.3% in the placebo group.

g. Aducanumab (Aduhelm) should be discontinued when patients progress to moderate to severe Alzheimer's disease since the medication has not been studied in more advanced settings. The following cognitive function scores (not all inclusive) represent moderate to severe impairment:

i. Clinical Dementia Rating (CDR) Global Score of 2 and above
ii. Mini Mental State Exam (MMSE) score of less than 19
iii. Montreal Cognitive Assessment (MoCA) score of 18 or less
iv. Quick Dementia Rating System (QDRS) score of 13 or less

h. Overall, the safety and efficacy of aducanumab (Aduhelm) remain highly uncertain based on conflicting phase 3 trial data and the unknown relationship between clearance of amyloid plaques and clinical improvement in Alzheimer's symptoms.

VIII. Lecanemab (Leqembi) clinical development:

a. Lecanemab (Leqembi) was studied in a double-blind, placebo-controlled, parallel-group dose-finding trial (Study 201) in adults (N= 856) with Alzheimer's disease. Participants had confirmed presence of amyloid pathology and MCI or mild dementia consistent with Stage 3 and Stage 4 disease.
   i. The primary clinical endpoint was the change from baseline in a cognitive composite measure, Alzheimer's Disease Composite Score (ADCOMS), at Week 53. Change from baseline in brain amyloid plaque as measured by PET and quantified by a composite standard uptake value ratio (SUVR) was assessed in a subset of patients at Week 53 and Week 79 and served as the endpoint to support accelerated approval.
   ii. Lecanemab (Leqembi) had a 64% likelihood of ≥25% slowing of progression on the primary endpoint relative to placebo at Week 53. However, this did not meet the prespecified success criterion of 80%.
   iii. Lecanemab (Leqembi) reduced brain amyloid plaque in a dose- and time-dependent manner. The 10 mg/kg biweekly arm had a statistically significant reduction in brain amyloid plaque from baseline to Week 79 compared to the placebo arm (mean difference of -0.31 SUVR or -73.5 Centiloids; $p<0.001$).
   iv. The most commonly reported adverse events in patients receiving treatment with Lecanemab (Leqembi) in Study 201 were infusion-related reactions (20% vs 3%), headache (14% vs 10%), ARIA-E (10% vs 1%), cough (9% vs 5%), and diarrhea (8% vs 5%).
   v. Patients were excluded from enrollment if they had baseline use of anticoagulant medications. However, antiplatelet medications such as aspirin and clopidogrel were allowed. The majority of patients on antithrombotic medications were on aspirin with limited data on the concomitant use of lecanemab (Leqembi) with other medications. Patients were also excluded if they had risk factors for intracerebral hemorrhage.

b. The phase 3 Clarity trial is underway and will be used to support an application for full approval in late 2023.

IX. Since there are no proven disease-modifying therapies for Alzheimer's disease to date, major advocacy and government bodies, such as the National Institutes of Health, U.S. Department of Health and Human Services, and the respective federal government portal of resources on Alzheimer's and related dementias at Alzheimers.gov, direct to clinical trial participation. Furthermore, the Centers for Medicare and Medicaid Services (CMS) only covers these therapies in the setting of a clinical trial. Patients participating in clinical trials receive regular care, often at leading healthcare facilities with experts in the field while participating in important medical research and further advancements in treatment with close safety

monitoring and follow-up. Participation in a clinical trial remains the most favorable treatment option for patients with Alzheimer's disease when available. At this time, the most likely place someone with Alzheimer's will be cured is within the setting of a clinical trial.

X. The following resources provide extensive information on available clinical trials for those with Alzheimer's disease:
   a. http://www.nia.nih.gov/alzheimers/clinical-trials
   b. https://www.alz.org/alzhimers-dementia/research_progress/clinical-trials
   c. https://clinicaltrials.gov

VI. Dosage/Administration

<table>
<tr><th>Indication</th><th>Dose</th></tr>
<tr><td colspan="2">aducanumab (Aduhelm)</td></tr>
<tr><td>Alzheimer's disease</td><td>Initial titration schedule:
<table>
<tr><th>IV Infusion (every 4 weeks)</th><th>Dosage (administered over approx. 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 initial titration, the recommended dosage is 10 mg/kg every four weeks and at least 21 days apart.</td></tr>
<tr><td colspan="2">lecanemab (Leqembi)</td></tr>
<tr><td>Alzheimer's disease</td><td>10 mg/kg that must be diluted then administered as an intravenous infusion over approximately one hour, once every two weeks</td></tr>
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VII. Billing Code/Availability Information

HCPCS code:

- J0172 – Injection, aducanumab-avwa, 2 mg; 1 billable unit = 2 mg
- J3590 – Unclassified biologicals

NDC:

- Aduhelm 170 mg/1.7 mL (100 mg/mL) single-dose vial – NDC 64406-101-01
- Aduhelm 300 mg/3 mL (100 mg/mL) single-dose vial – NDC 64406-102-02
- Leqembi 200 mg/2 mL (100 mg/mL) solution in an SDV: 62856-0212-xx
- Leqembi 500 mg/5 mL (100 mg/mL) solution in an SDV: 62856-0215-xx

VIII. References

1. Aduhelm [package insert]. Cambridge, MA; Biogen Inc; July 2021.
2. Leqembi [package insert]. Nutley, NJ; Eisai Inc; January 2023.
3. Product Dossier. "Unapproved Product Formulary Submission Dossier: Aducanumab in Mild Cognitive Impairment due to Alzheimer's Disease and Alzheimer's Disease Dementia. Biogen Inc. September 5, 2020.
4. Product Dossier. "Academy of Managed Care Pharmacy (AMCP) Approved Product Dossier for LEQEMBI™ (lecanemab-irmb) for intravenous use. Eisai Inc, February 2023.
5. McKhann M.G. 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 May; 7(3): 263-269.
6. Lin GA, Whittington MD, Synnott PG, McKenna A, Campbell J, Pearson SD, Rind DM. Aducanumab for Alzheimer's Disease: Effectiveness and Value; Draft Evidence Report. Institute for Clinical and Economic Review, May 5, 2021. https://icer.org/assessment/alzheimers-disease-202
7. Langa, LM, Levine DA. The Diagosis and Management of Mild Cognitive Impairment: A clinical Review
8. Alzheimer's Home Page: National Institute on Aging. Alzheimers.gov. https://www.alzheimers.gov/. Accessed on July 16, 2021.
9. Participating in Alzheimer's disease Research. National Institute on Aging. https://www.nia.nih.gov/health/participating-alzheimers-disease-research. Accessed on July 16, 2021.