Anti-amyloid-β monoclonal antibodies:

donanemab-azbt (Kisunla); lecanemab-irmb (Leqembi)

Date of Origin: 06/23/2021 **Last Review Date: 03/26/2025** **Effective Date: 03/26/2025**

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Developed By: Medical Criteria Committee

I. Length of Authorization

- N/A

II. Dosing Limits

- N/A

III. Initial Approval Criteria

- Donanemab (Kisunla) 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. Donanemab (Kisunla) 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, the population in which treatment was initiated in clinical trials. 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.
   a. Please note that aducanumab (Aduhelm) was discontinued in January 2024 and the ENVISION clinical study, which was aimed to confirm the clinical benefit of aducanumab (Aduhelm) following the accelerated approval in 2021, was terminated. Historical information related to this therapy is included in this policy for a holistic view of the class and clinical information to date.

II. The amyloid beta-directed antibodies have had long and complicated approval histories, including FDA unfavorable FDA Advisory Committee meetings, complete response letters (CRLs), and accelerated approvals based on the reduction of amyloid beta plaques observed in those treated. Since its original accelerated approval, aducanumab (Aduhelm) has been discontinued without completion of the confirmatory trial. Lecanemab (Leqembi) received accelerated approval in January 2023, and later was granted a traditional approval in July 2023 based on data from the confirmatory Phase 3 CLARITY trial. Donanemab (Kisunla) received full approval in July 2024 based on the Phase 3 TRAILBLAZER-ALZ 2 study.

III. Despite FDA approval of some of these therapies, a clinically meaningful benefit in outcomes such as, but not limited to improved quality of life, social and emotional functioning, and ability to perform essential activities of daily living, have not been established.

IV. **Aducanumab (Aduhelm) clinical development**

Included for historical background only, and to provide information related to the class of medications holistically.

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.

V. **Lecanemab (Leqembi) clinical development:**

a. Lecanemab (Leqembi) was originally 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 <u>not</u> 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 was used to support traditional approval in July 2023. This study included 1,795 patients randomized to receive lecanemab (Leqembi) or placebo. Like Study 201, the primary endpoint included the change from baseline at 18 months in the CDR-SB.

i. Treatment with lecanemab (Leqembi) met the primary endpoint and reduced clinical decline on the global cognitive and functional scale, the CDR-SB, compared to placebo (-0.45 [-27%], *P<0001*). However, this change in CDR-SB is less than the 1 to 2 point change that has been established as the minimal clinically important difference.

c. Overall, the results from the lecanemab (Leqembi) clinical trial program demonstrate improvements in amyloid plaque reduction and trend towards improvement in cognitive function. However, the relationship between plaque reduction and clinical improvement/impact on clinically meaningful outcomes has not been established, and the modest improvement in CDR-SB does not meet the minimum threshold for providing an impactful clinical difference compared to placebo. Further, there remains significant safety considerations that may outweigh the evolving potential benefit of treatment.

VI. **Donanemab (Kisunla) clinical development**

a. Donanemab (Kisunla) was evaluated in the TRAILBLAZER-ALZ-2 Phase 3, double-blind, placebo-controlled study that included 1,736 patients with early (Stage 3 and Stage 4) AD, as confirmed by the presence of amyloid pathology and MCI or mild dementia state of disease. Patients were analyzed based on two primary analysis populations: 1) tau levels of either low/medium or 2) a combination of low/medium plus high tau levels.

b. The primary endpoint was change in integrated Alzheimer's disease Rating Scale (iADRS) score from baseline to week 76. The iADRS is a combination of two scores: the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog13) and the Alzheimer's disease Cooperative Study – instrumental Activities of Daily Living (ADCS-iADL) scale. The total score ranges from 0 to 144, with lower scores reflecting worse cognitive and functional performance.

c. The study population consisted of adults with gradual, progressive changes in memory function for at least six months, MMSE score of 20-28 at baseline, met 18F flortaucipir PET scan criteria. Participants required a study partner who provided written informed consent to participate.

d. Patients treated with donanemab (Kisunla) achieved a statistically significant reduction in clinical decline on the iADRS compared to placebo after 76 weeks in the combined population (2.92, p<0.0001) and the low/medium tau population (3.25, p<0.0001).

i. While the primary outcome was statistically significant, the clinical meaningfulness of these results is uncertain since the minimal clinically important difference (5 points in AD with mild cognitive impairment and 9 points in AD with mild dementia) was not met. Further, there remains significant safety considerations that may outweigh the evolving potential benefit of treatment.

VII. 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. 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.

VIII. 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

Indication	Dose
donanemab (Kisunla)	
Alzheimer's disease	The recommended dosage of Kisunla is 700 mg administered as an intravenous infusion over approximately 30 minutes every four weeks for the first three doses, followed by 1,400 mg every four weeks thereafter.
lecanemab (Leqembi)	
Alzheimer's disease	The recommended dosage of Leqembi is 10 mg/kg administered as an intravenous infusion over approximately one hour, every two weeks

VII. Billing Code/Availability Information

HCPCS code:

- J0175 – Injection, donanemab-azbt, 2mg: 1 billable units = 2 mg
- J0174 – Injection, lecanemab-irmb, 1mg; 1 billable unit = 1 mg

NDC:

- Kisunla 350 mg/20 mL (17.5 mg/mL) solution in a single-dose vial: 00002-9401-xx
- 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

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3. Kisunla [package insert]. Indianapolis, IN; Eli Lilly; July 2024
4. 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.
5. Product Dossier. "Academy of Managed Care Pharmacy (AMCP) Approved Product Dossier for LEQEMBI™ (lecanemab-irmb) for intravenous use. Eisai Inc, February 2023.
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