DR.011.E IgG1 Monoclonal Antibodies for Alzheimer's

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PRODUCT VARIATIONS

This policy applies to all Jefferson Health Plans/Health Partners Plans lines of business unless noted below.

POLICY STATEMENT

We consider Kisunla™ ™ (donanemab-azbt), Leqembi™(lecanemab-irmb) and any newly approved drugs in this class medically necessary for its FDA approved indications when the prior authorization criteria listed in this policy are met.

OFF-LABEL USE

Authorization for off-labeled use of medication will be evaluated on an individual basis. Review of an off-labeled request by the Medical Staff will be predicated on the appropriateness of treatment and full consideration of medical necessity. For off-label use Medical Directors will review scientific literature and local practice patterns.

FDA APPROVED INDICATIONS

Leqembi™ and Kisunla™ ™ are humanized immunoglobulin gamma 1 monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta indicated for the treatment of:

- Alzheimer's disease
    - This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with KISUNLA™ or LEQEMBI™. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

PRIOR AUTHORIZATION CRITERIA

INITIAL CRITERIA

Initial use of Leqembi™ and Kisunla™ ™ may be considered medically necessary when All of the following apply:

1. FDA approved age is 50 years old or older.
2. Must have documentation of a genetic mutation and/or documentation of Alzheimer's disease. *(Documentation must be attached).*
3. Must have documentation of a diagnosis of Alzheimer's disease of mild severity (a MMSE score between 24 and 20 or a CDR-SB score of 0.5 to 1).
4. Must have no contraindications to the requested drug, its components (no history of hypersensitivity to the requested drug), or a contraindication to MRI scanning (e.g. cardiac pacemaker/defibrillator or ferromagnetic metal implants)
5. Must have no medical or neurological condition that may be contributing to cognitive impairment.
6. Must have no history of a stroke, TIA, seizures, or unexplained loss of consciousness in the past year.
7. If requesting for Kisunla™, must have no history of unstable angina, MI, advanced chronic HF, or clinically significant conduction abnormalities for $\geq$ 1 year.
8. Must have no history of brain hemorrhage, bleeding disorder, cerebrovascular abnormalities or on blood thinners other than prophylactic dose aspirin.
9. Must have recent (within the last year) PET scan showing presence of beta-amyloid plaque and/or CSF testing, showing presence of tau protein? (Attach results).
10. The medication is prescribed by or in consultation with a physician who is a psychiatrist, neurologist, geriatrician, or neuropsychiatrist, and the documentation reflects that the patient will be monitored at least once every 3 months.
11. Must confirm that all other causes of dementia are ruled out? (Vascular dementia, Lewy body dementia (DLB), Frontotemporal dementia (FTD), Parkinson's disease dementia)
12. The prescription is consistent with the FDA approved package labeling.
13. Must not be used in combination with any other amyloid beta-directed antibodies.
14. If the patient has a recent MRI scan (within one year to initiating treatment) with results attached, **approve for 6 months.**

RENEWAL CRITERIA

1. The patient continues to meet the diagnostic criteria after initial treatment with the requested drug for Alzheimer's.

2. The patient does not have unacceptable toxicity which precludes safe administration of the drug.
    a. (Examples of unacceptable toxicity include the following: ARIA-E (cerebral edema) excluding mild ARIA-E on MRI and asymptomatic or has mild clinical symptoms ARIA-H (hemosiderin deposition) excluding mild ARIA-H on MRI and asymptomatic).

3. The patient obtained an MRI after the 5th dose and will have an MRI prior to the 7th, 9th and 14th infusions.
    a. There are no observed ARIA, showing 10 or more new incident microhemorrhages or > 2 focal areas of superficial siderosis (radiographic severe ARIA-H) and/ or the MRI is showing radiographic stabilization (i.e., no increase in size or number of ARIA-H) with results attached.

4. If patient has been on treatment for less than 12 months, approve for the duration of 6 months.

5. If the patient has been on the treatment for greater than 12 months and the patient shows clinical benefit (stabilization) (Attach notes), approve for the duration of 6 months.

DOSAGE AND ADMINISTRATION

Donanemab-azbt (Kisunla™) is available as a single-use dose vial containing 350 mg/20 mL (17.5 mg/mL) for intravenous infusion. Lecanemab-irmb (Leqembi™) is available as either 500 mg/5 mL or 200 mg/2 mL (both 100mg/mL) solution in a single-dose vial for intravenous infusion or 360 mg/1.8 mL (200 mg/mL) in a single-dose prefilled IQLIK autoinjector for subcutaneous injection. Dilution to a final concentration of 4-10 mg/mL with 0.9% Sodium Chloride for donanemab-azbt (Kisunla™). Dilution in 250 mL of 0.9% Sodium Chloride for lecanemab-irmb (Leqembi™) is required prior to administration. Infusing through an IV line containing a sterile, low-protein binding, 0.2 micron in-line filter is required for lecanemab-irmb (Leqembi™). Must confirm the presence of amyloid beta pathology prior to initiating treatment for both donanemab-azbt (Kisunla™) and lecanemab-irmb (Leqembi™).

Dosing recommendations for Alzheimer's disease:

Leqembi™:

- Recommended dose for LEQEMBI™ is 10 mg/kg once every 2 weeks as an intravenous (IV) infusion over approximately one hour, for 18 months.
- After 18 months, continue treatment once every 2 weeks or transition to an intravenous or subcutaneous maintenance dosing regimen.
    - Recommended maintenance dosage:
        - Intravenous infusion: 10 mg/kg once every 4 weeks
        - Subcutaneous injection: 360 mg administered once a week using LEQEMBI™ IQLIK autoinjector.
- Obtain a recent brain MRI before initiating treatment, then obtain an MRI approximately 1 week before the 3rd, 5th, 7th, and 14th infusions. If radiographically observed ARIA occurs, treatment recommendations are based on type, severity, and symptoms present.

Kisunla™ ™:

- Recommended dosage of Kisunla™ is shown on the table below (see Table 1). KISUNLA™ is administered as an (IV) over approximately 30 minutes every four weeks.
- Consider stopping dosing of Kisunla™ based on reduction of amyloid plaques to minimal levels on amyloid PET imaging.
- Obtain a recent baseline brain MRI prior to initiating treatment; obtain an MRI prior to 2nd, 3rd, 4th, and 7th infusions. If radiographically observed ARIA occurs, treatment recommendations are based on type, severity, and symptoms present.

Table 1. KISUNLA Dosing

IV Infusion (every 4 weeks)	KISUNLA™ Dosage (Administered over approximately 30 minute)
Infusion 1	350 mg
Infusion 2	700 mg
Infusion 3	1,050 mg
Infusion 4 and beyond	1, 400 mg

RISK FACTORS/SIDE EFFECTS

- **Amyloid Related Imaging Abnormalities (ARIA)** Enhanced clinical vigilance for ARIA is recommended during the first 24 weeks of treatment with KISUNLA™ and the first 14 weeks of treatment with LEQEMBI™, particularly during titration. If a patient experiences symptoms which could be suggestive of ARIA (e.g., headache, altered mental status, dizziness, visual disturbance, nausea), clinical evaluation should be performed, including MRI testing if indicated.

- **Hypersensitivity Reactions**: Angioedema and urticaria have occurred with KISUNLA™ and angioedema, bronchospasm, and anaphylaxis have occurred with LEQEMBI™. If a hypersensitivity reaction occurs, promptly discontinue the infusion of KISUNLA™ and LEQEMBI™ and initiate appropriate therapy.

- **Infusion-Related Reactions:** Infusion rate of Leqemb™ may be reduced or discontinued if infusion reaction occurs. Pre-medication of antihistamines, NSAIDs, or corticosteroids is considered.

- The most common adverse reactions of Kisunla™: ARIA-E, ARIA-H microhemorrhage, ARIA-H superficial siderosis, and headache.

MONITORING

Efficacy

- Physical Findings
    - ADAS-Cog 13 (Alzheimer's disease Assessment Scale-Cognitive Subscale 13).
    - Aβ PET composite SUVR (Beta-amyloid positron emission tomography.
    - Baseline and periodic monitoring of MRI.
    - CDS-SB (Clinical Dementia Rating-Sum of Boxes).
    - MMSE score (Mini0Mental State Examination).
    - Standardized uptake value ratio.

Safety

- Look for signs and symptoms stated above in the Risk Factors/Side Effects section to ensure safety.

BLACK BOX WARNING

Kisunla™ and Leqembi™: Amyloid Related Imaging Abnormalities (ARIA) can occur in early treatment and is typically asymptomatic. Patients who are apolipoprotein E ε4 (ApoE ε4) homozygotes have a higher incidence of ARIA. Testing for ApoE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA.

CLINICAL EVIDENCE

LEQEMBI™

The efficacy of LEQEMBI (lecanemab-irmb) was evaluated in two double-blind, placebo-controlled, parallel-group, randomized studies (Study 1, NCT01767311; Study 2 NCT03887455) in patients with Alzheimer's disease (patients with confirmed presence of amyloid pathology and mild cognitive impairment, or mild dementia). In both studies, patients with a Clinical Dementia Rating (CDR) global score of 0.5 or 1.0 and a Memory Box score of 0.5 or greater were enrolled. All participants had a Mini-Mental State Examination (MMSE) score of ≥22 and ≤30 and an objective impairment in episodic memory as indicated by at least 1 standard deviation below age-adjusted mean in the Wechsler-Memory Scale-IV Logical Memory II (subscale) (WMS-IV LMII). Patients were enrolled with or without concomitant approved therapies (cholinesterase inhibitors and the N-methyl-D-aspartate antagonist memantine) for Alzheimer's disease. The dosage of 10 mg/kg once every 2 weeks was administered by intravenous infusion was assessed in the 18 months placebo-controlled part of Study 1 and Study 2 and was continued in the optional long-term extension in each study. Participants were transitioned to an intravenous dose of 10 mg/kg once every 4 weeks or subcutaneous 360 mg every week after 18 months.

In Study 1, 856 patients were randomized to receive one of five doses of intravenous LEQEMBI or placebo, with 161 patients assigned to the recommended dose of 10 mg/kg every two weeks. Initially, 71.4% of

participants were ApoE ε4 carriers, but due to a protocol amendment, carriers were no longer randomized to the recommended dose arm. Those who had received the dose for six months or less were discontinued, resulting in only 30.3% ApoE ε4 carriers in that group. A subgroup of 315 patients participated in an amyloid PET sub study, with 277 evaluated at Week 79. The primary endpoint was the change from baseline at Week 53 using a composite cognitive score (CDR-SB, MMSE, ADAS-Cog14). LEQEMBI showed a 64% likelihood of achieving at least a 25% slowing in disease progression compared to placebo, which did not meet the prespecified success criterion of 80%. At Week 79, secondary endpoints showed less decline in cognitive scores for LEQEMBI-treated patients compared to placebo, with a 26% slowing in CDR-SB and 47% in ADAS-Cog14. Following the 79-week double-blind phase, patients could enter an open-label extension lasting up to 260 weeks, after a treatment gap averaging 24 months.

In Study 2, 1,795 patients were randomized 1:1 to receive LEQEMBI 10 mg/kg or placebo every two weeks. Of these, 69% were ApoE ε4 carriers and 31% were non-carriers. Randomization was stratified by disease stage, use of Alzheimer's therapies, ApoE ε4 status, and geographic region. The primary efficacy outcome was the change in CDR-SB at 18 months, where LEQEMBI significantly reduced clinical decline by 27% compared to placebo (−0.45, $P < 0.0001$). Statistically significant improvements were also observed in secondary endpoints, including ADAS-Cog14 and ADCS MCI-ADL. Both ApoE ε4 carriers and non-carriers benefited from treatment. Starting at six months, LEQEMBI consistently showed statistically significant benefits across all time points for both primary and key secondary endpoints.

KISUNLA™

The efficacy of KISUNLA (donanemab-azbt) was evaluated by in a double-blind, placebo-controlled, parallel group study (Study 1, NCT04437511) which assessed the Dosing Regimen 1 (700 mg every 4 weeks for the first 3 doses, and then 1,400 mg every 4 weeks) in patients with Alzheimer's disease (patients with confirmed amyloid pathology and mild cognitive impairment or mild dementia). Patients enrolled in Study 1 had a Mini-Mental State Examination (MMSE) score of ≥20 and ≤28 and had a progressive change in memory function for at least 6 months. Participants were included based on visual assessment of tau PET imaging with flortaucipir and standardized uptake value ratio (SUVR). They were also enrolled with or without concomitant approved therapies (cholinesterase inhibitors and the N-methyl-D-aspartate antagonist memantine) for Alzheimer's disease. Participants could enroll in an optional, long-term extension study. Study 2 (NCT05738486) was a randomized, double-blind study that assessed the different titration regimens on ARIA-E and change from baseline in amyloid in adult patients with Alzheimer's disease, including Dosing Regimen 2 (doses every 4 weeks with 350 mg the first infusion, 700 mg the second infusion, 1,050 mg the third infusion, and then 1,400 mg every 4 weeks) that demonstrated comparable pharmacodynamic effects on amyloid plaque reduction with reduced ARIA-related incidents compared to Dosing Regimen 1. The Inclusion and exclusion criteria of Study 2 were the same as Study 1, except that tau PET was not an inclusion criterion.

In Study 1, 1,736 patients were randomized 1:1 to receive either 700 mg of KISUNLA or placebo for up to 72 weeks. Treatment was adjusted based on amyloid PET imaging at Weeks 24, 52, and 76, with patients eligible to switch to placebo if their amyloid levels dropped below specific thresholds. Dose adjustments were also made in response to treatment-emergent ARIA detected via MRI. The primary efficacy endpoint was the change in the integrated Alzheimer's Disease Rating Scale (iADRS) score at Week 76, which combines cognitive and functional assessments. Statistically significant reductions in clinical decline were observed in both the combined tau population and the low/medium tau subgroup. Additional measures,

including CDR-SB, ADAS-Cog13, and ADCS-iADL, also showed significant improvements with KISUNLA compared to placebo. By Week 76, 69% of patients met the criteria to switch to placebo based on amyloid PET results. However, amyloid levels may rise after treatment cessation, and there is no data beyond 76 weeks to determine the need for continued dosing.

In Study 2, patients were randomized in equal groups to receive one of four dosing regimens, including Dosing Regimen 1 (N=207) and Dosing Regimen 2 (N=212), with treatment lasting up to 72 weeks. The criteria for stopping treatment based on amyloid PET imaging were consistent with those used in Study 1. ApoE ε4 carriers made up 65% of this group, including 55% heterozygotes and 10% homozygotes, while 36% were non-carriers. The primary endpoint of Study 2 was the proportion of patients experiencing ARIA-E (amyloid-related imaging abnormalities with edema), and results showed a lower incidence of ARIA-E in patients on Dosing Regimen 2 compared to those on Dosing Regimen 1 by Week 52. ARIA-E occurred more frequently in ApoE ε4 homozygotes than in heterozygotes, with the lowest incidence in non-carriers. However, due to the small number of events and limited exposure within ApoE ε4 subgroups, definitive conclusions about ARIA-E risk could not be drawn.

BACKGROUND

ALZHEIMER'S DISEASE

Alzheimer's disease is a neurodegenerative disorder resulting in progressive cognitive and behavioral decline. Alzheimer's disease is the leading cause of dementia, a general term for memory loss and cognitive decline, accounting for 60% to 80% of cases. Estimating to affect 5.8 million Americans, or 10% if people 65 years old or older, with 80% being older than 75 years old. Additionally, 200,000 Americans have early-onset Alzheimer's disease, defined as Alzheimer's disease affecting those younger than 65 years old. Due to the aging population, the estimated number of people aged 65 years and older with Alzheimer's disease is estimated to be 13.8 million in the United States in 2050, barring any developments in therapies. Alzheimer's disease is the sixth leading cause of death in the United States and the fifth leasing cause of death among those age 65 years and older. Almost two-thirds of Americans with Alzheimer's disease are women. African Americans and Latino Americans are twice as likely and one and half times as likely, respectively to have Alzheimer's disease as older White Americans. On average, patients survive approximately 4 to 8 years after diagnosis, with survival time affected by age at diagnosis and severity of other medical conditions.

The pathogenesis of Alzheimer's disease has been attributed to extracellular aggregates of beta-amyloid plaques and intracellular neurofibrillary tangles in the cortical and limbic areas of the human brain. Beta-amyloid peptides are created through the proteolytic cleavage of the amyloid precursor protein; this process likely instigates the intraneuronal accumulation of phosphorylated tau, which is the primary component of the neurofibrillary tangles. It is estimated that beta-amyloid plaques begin to develop 10 years to 30 years before Alzheimer's disease onset, while neuronal degeneration, such as the presence of tau in the cerebrospinal fluid, may develop shortly before clinical symptoms first appear. Both biomarkers of Alzheimer's disease can be detected in the CSF and by positron emission computed tomography (PET).

Aside from increasing age, which is the greatest risk factor for Alzheimer's disease, the two other major risk factors are family history and genetics (risk genes and deterministic genes, the latter being genes that

cause the disease rather than genes that increase the risk for disease development). Familial Alzheimer's disease has mainly been associated with mutation in APP and presenilin genes PSEN1 and PSEN2/ Comparatively, non-familial or sporadic-onset Alzheimer's disease has a complex etiology, involving genetic, environmental, metabolic, viral, and other factors. The E4 variant of apolipoprotein E is the main susceptibility gene for Alzheimer's disease, while the E2 variant of APOE is considered a protective factor that reduces the incidence of Alzheimer's disease and beta-amyloid accumulation and delays the age of Alzheimer's disease onset. Acquired risk factors include but are not limited to head trauma, hypertension, cerebrovascular disease, hypercholesteremia, and environment risk factors (lead, pesticides). Conversely, higher education and socioeconomic status have been associated with lower age-adjusted incidence of Alzheimer's disease diagnosis.

Alzheimer's disease is characterized by memory loss and progressive neurocognitive dysfunction. Signs and symptoms include memory loss that disrupts daily life; challenges in planning or problem-solving; difficulty completing familiar tasks at home, work, or at leisure; confusion with orientation to time or place; difficulty with visual images and spatial relationships; difficulties with speaking or writing; decreased or poor judgment; withdrawal from work or social activities; and changes in mood and personality/ Individuals may present with one or more of these symptoms and in varying degree of severity, as listed below.

1. Clinical Dementia Rating (CDR)-Global Score
    a. 0 = Normal
    b. 0.5 = Very Mild Dementia
    c. 1 = Mild Dementia
    d. 2 = Moderate Dementia
    e. 3 = Severe Dementia

2. Mini-Mental Examination Status (MMSE)
    a. 25 - 30 suggest normal cognition
    b. 20 – 24 suggests mild dementia
    c. 13 – 20 suggests moderate dementia
    d. Less than 12 suggests severe dementia.

3. Montreal Cognitive Assessment (MoCA)
    a. Mild Cognitive Impairment: 19 – 25
    b. Mild Alzheimer's Disease: 11 – 21
    c. Normal: 26 and above

CODING

Note: The Current Procedural Terminology (CPT®), Healthcare Common Procedure Coding System (HCPCS), and the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes that *may* be listed in this policy are for reference purposes only. Listing of a code in this policy does not imply that the service is covered and is not a guarantee of payment. Other policies and coverage guidelines may apply. When reporting services, providers/facilities should code to the highest level of specificity using the code that was in effect on the date the service was rendered. This list may not be all inclusive.

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CPT Code	Description
99483	Cognition-focused evaluation including a pertinent history and examination

HCPCS Code	Description
J0174	Legembi (lecanemab-irmb 1mg)
J0175	Injection, donanemab-azbt, 2 mg
G0336	PET imaging brain Alzheimer's

ICD-10 Codes	Description
G30	Alzheimer's disease
G30.0	Alzheimer's disease with early onset
G30.1	Alzheimer's disease with late onset

DISCLAIMER

Approval or denial of payment does not constitute medical advice and is neither intended to guide nor influence medical decision making. Policy Bulletins are developed to assist in administering plan benefits and constitute neither offers of coverage nor medical advice. This Policy Bulletin may be updated and therefore is subject to change.

For Health Partners Plans Medicaid and Health Partners Plans Chip products: Any requests for services that do not meet criteria set in PARP will be evaluated on a case-by-case basis.

POLICY HISTORY

This section provides a high-level summary of changes to the policy since the previous version.

Summary	Version	Version Date
2025 Ad-hoc review. Drug name added, Revisions to Prior authorization Criteria, Dosage& Administrations, Risk Factor/Side effects, Coding and Clinical Evidence sections. References updated.	E	12/17/2025
2025 Annual Review. Revisions to Dosage, Risk Factors and Side Effects, and Black Box Warning. References updated accordingly.	D	05/17/2024
2024 Annual review. Prior authorization and renewal criteria were updated.	D	05/17/2024
July 2023 Ad-hoc code update. J0174 was added to the coding table for the drug Legembi (lecanemab-irmb, 1 mg) J3590 was removed.	C	07/01/2023
2023 Annual review. Title of policy changed from: Aduhelm™ (aducanumab-avwa) to IgG1 Monoclonal Antibodies for Alzheimer's. Revisions made to include the drug Legembi (lecanemab-irmb). Prior authorization and renewal criteria were revised. Code J0172 was added to the coding table. References were updated accordingly.	C	05/24/2023
2022 Annual review. Renewal criteria and disclaimer sections were updated.	B	09/01/2022
This is a new drug policy.	A	11/01/2021

REFERENCES

1. Albert M, DeKosky S, 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. Alzheimer's Dement. 2011; 7(3): 270-279. Doi: 10.1016/j.jalz.2011.03.008.

2. Alzheimer's Association (AA). Causes and risk factors for Alzheimer's disease: https://www.alz.org/alzheimers-dementia/what-is-alzheimers/causes-and-risk-factors

3. UpToDate: Treatment of Alzheimer Disease Authors: Daniel Press, MD; Stephanie S Buss, MD-last update September, 30, 2021, Literature review February, 2024 https://www.uptodate.com/contents/treatment-of-alzheimer-disease?search=alzheimer%20treatment&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H3053641237

4. Leqembi™ (lecanemab-irmb) Prescribing Information. Eisai and Biogen; August 2025. Accessed October 9, 2025.

5. Kisunla™ (donanemab-azbt) Prescribing Information. Eli Lilly and Company; August 2025. Accessed October 9, 2025.