CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Neurology – Kisunla Utilization Management Medical Policy
- Kisunla™ (donanemab-azbt intravenous infusion – Lilly)

REVIEW DATE: 07/16/2025

OVERVIEW
Kisunla, an amyloid beta-directed antibody, is indicated for the treatment of **Alzheimer's disease** in patients with mild cognitive impairment or mild dementia stage of disease.[1]

Disease Overview
An estimated 7.2 million Americans ≥ 65 years of age are living with Alzheimer's dementia in 2025, with 74% of these people ≥ 75 years of age.[2] The number and proportion of older adults who have mild cognitive impairment due to Alzheimer's disease is difficult to estimate; however, a rough approximation suggests that 5 to 7 million older Americans may have mild cognitive impairment due to Alzheimer's disease. People with mild cognitive impairment due to Alzheimer's disease have biomarker evidence of brain changes due to the disease in addition to subtle problems with memory and thinking. Biomarker evidence includes abnormal levels of amyloid beta as evidenced on positron emission tomography (PET) scans and in analysis of cerebrospinal fluid, and decreased metabolism of glucose as shown on PET scans. These cognitive problems may be noticeable to the individual family members and friends, but not to others, and they do not interfere with the person's ability to carry out everyday activities. The mild changes in cognitive abilities occur when the brain can no longer compensate for the damage and death of nerve cells due to Alzheimer's disease.

Clinical Efficacy
The current Kisunla efficacy information is insufficient to determine if the medication demonstrates any clinically meaningful benefits. In the absence of additional clinical trials, there is not enough information to support approval.

POLICY STATEMENT
Due to safety concerns and the lack of clinically significant efficacy data, **approval is not recommended** for Kisunla. The current Kisunla efficacy information is insufficient to determine if the medication demonstrates any clinically meaningful benefits; whereas, safety concerns have been demonstrated in clinical trials. In the absence of additional clinical trials, there is not enough information to support approval.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA
None.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kisunla is not recommended in the following situations:

1. **Alzheimer's Disease.** Due to the lack of clinically significant efficacy data, approval is not recommended for Kisunla.

   The efficacy of Kisunla for traditional approval was evaluated in one Phase III randomized, double-blind, placebo-controlled, multicenter, pivotal study (TRAILBLAZER-ALZ2) in patients with mild cognitive impairment due to Alzheimer's disease and mild Alzheimer's disease dementia (n = 1,736).[3] The primary efficacy endpoint was the change from baseline in the integrated Alzheimer's Disease Rating Scale (iADRS) at 76 weeks, an assessment of cognition and daily function with scores ranging from 0 to 144 (lower scores indicate greater impairment). A key secondary endpoint included the change from baseline at 76 weeks in the Clinical Dementia Rating Scale – sum of boxes (CDR-SB), also an assessment of cognition and daily function with scores ranging from 0 to 18 (higher scores indicate greater impairment). For the low/medium tau population, the least-squares mean (LSM) change from baseline at Week 76 in the iADRS score was -6.02 in the Kisunla arm and -9.27 in the placebo arm (treatment difference 3.25; $P < 0.001$). In the combined (low/medium and high tau) population, the LSM change from baseline at Week 76 in the iADRS score was -10.19 in the Kisunla arm and -13.11 in the placebo arm (treatment difference 2.92; $P < 0.001$). In the low/medium tau population, the placebo-adjusted LSM change from baseline at 76 weeks for CDR-SB was -0.67, and in the combined population, the placebo-adjusted LSM change from baseline at 76 weeks for CDR-SB was -0.70. However, this slowing of progression did not achieve clinical significance. The authors of TRAILBLAZER-ALZ2 note that the minimal clinically important difference for the iADRS is a change of 5 points for those with Alzheimer disease with mild cognitive impairment and 9 points for those with Alzheimer disease with mild dementia, and it is 1 to 2 points for the CDR-SB.[3,4]

   Additionally, one Phase II, randomized, double-blind, placebo-controlled, multicenter study (TRAILBLAZER-ALZ) was conducted in patients with mild cognitive impairment due to Alzheimer's disease and mild Alzheimer's disease dementia (n = 257).[5] The change from baseline in the iADRS score at 76 weeks was -6.86 in the Kisunla arm and -10.06 in the placebo arm (treatment difference 3.20; $P = 0.04$). The placebo-adjusted change from baseline at 76 weeks for the CDR-SB score was -0.36 and failed to show a significant difference between the two trial groups.

   Kisunla can cause amyloid related imaging abnormalities-edema (ARIA-E) and amyloid related imaging abnormalities-hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis, which can be observed on magnetic resonance imaging (MRI).[1] A recent (within 1 year) MRI of the brain should be obtained prior to initiating treatment with Kisunla. The safety of Kisunla has not been evaluated in patients with prior cerebral hemorrhage > 1 cm in greatest diameter, more than four microhemorrhages, more than one area of superficial siderosis, severe white matter disease, and vasogenic edema. Enhanced clinical vigilance for asymptomatic amyloid related imaging abnormalities (ARIA) is recommended during the first four doses of treatment with Kisunla, particularly during titration, because the majority of ARIA was observed during this time. MRIs of the brain should be obtained prior to the second, third, fourth, and seventh infusions of Kisunla to evaluate for the presence of asymptomatic ARIA. In addition to ARIA, intracerebral hemorrhages > 1 cm in diameter have occurred in patients treated with Kisunla. Symptomatic ARIA occurred in 6% of patients treated with Kisunla (n = 52/853) in the pivotal trial, and clinical symptoms associated with ARIA resolved in approximately 85% of affected patients (n = 44/52). Including asymptomatic radiographic events, ARIA was observed in 36% of patients treated with Kisunla vs. 14% of patients treated with

placebo in the pivotal trial. ARIA-E and ARIA-H were observed in 24% and 31% of patients treated with Kisunla vs. 2% and 13% of patients receiving placebo.

TRAILBLAZER-ALZ 6, an ongoing, randomized, double-blind, Phase IIIb study in early symptomatic Alzheimer's disease, was undertaken to compare the standard Kisunla dosing regimen with three alternative dosing arms (n = 843).[6] A lower incidence of ARIA occurred with the modified titration dosing regimen administered in TRAILBLAZER-ALZ 6 (infusions 1 through 4: 350 mg/700 mg/1,050 mg/1,400 mg) vs. the regimen administered in the pivotal trial (infusions 1 through 4: 700 mg/700 mg/700 mg/1,400 mg); therefore, the modified titration dosing regimen is now recommended for administration of Kisunla.[1] In TRAILBLAZER-ALZ 6, symptomatic ARIA-E occurred in 3% of patients and symptomatic ARIA-H occurred in < 1% of patients through 12 months of treatment with Kisunla. Clinical symptoms associated with ARIA-E resolved in approximately 67% of patients at 12 months. Including asymptomatic radiographic events, ARIA, ARIA-E, and ARIA-H were observed in 29%, 16%, and 25% of patients treated the modified titration dosing regimen, respectively.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Kisunla™ intravenous infusion [prescribing information]. Indianapolis, IN: Lilly; July 2025.
2. Alzheimer's Association. Alzheimer's disease facts and figures-2025. Available at: https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf. Accessed on July 14, 2025.
3. Sims JR, Zimmer JA, Evans CD, et al, for the TRAILBLAZER-ALZ 2 Investigators. Donanemab in early symptomatic Alzheimer disease: The TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA*. 2023;330(6):512-527.
4. Andrews JS, Desai U, Kirson NY, et al. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. *Alzheimers Dement*. 2019;5:354-363.
5. Mintun MA, Lo AC, Duggan Evans C, et al. Donanemab in early Alzheimer's disease. *N Engl J Med*. 2021;384(18):1691-1704.
6. Wang H, Serap Monkul Nery E, Ardayfio P, et al. Modified titration of donanemab reduces ARIA risk and maintains amyloid reduction. *Alzheimers Dement*. 2025;21(4):e70062.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	07/24/2024
Annual Revision	No criteria changes.	07/16/2025