PART B DRUG MEDICAL/PHARMACY	ASPIRE HEALTH	**Effective Date** December 15, 2024	
		Policy # Kisunla (donanemab-azbt)	
	Kisunla (donanemab-azbt)	**Review Date** 8/27/2024	**Applicable to:** ☑ Medicare Advantage ☐ Commercial ☐ Elevance Health HMO ☐ Blue Shield Trio
	Approver's Name & Title QI & UM Drug Subcommittee		

Aspire Health Plan applies medical drug clinical criteria as a reference for medical policy information only. Federal and state laws or requirements, contract language, and Plan benefit may take precedence over the application of these clinical criteria. Please consult the applicable certificate or contract for benefit details. This policy is subject to revision at the discretion of the Plan and is therefore subject to change. Refer to the disclaimer section below for more information.

POLICY

This policy addresses the coverage of Kisunla (donanemab-azbt), an amyloid beta-directed antibody indicated for the treatment of Alzheimer's disease (AD). Specifically, the label indicates, "treatment with Kisunla should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials."

Aspire Health Plan adheres to Medicare guidelines and coverage determinations will be in compliance with the National Coverage Determination (NCD) issued by Centers for Medicare and Medicaid Services (CMS) effective 12/12/2022 .

Effective for dates of service on and after July 2, Medicare covers Kisunla under NCD 200.3 - Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (AD).

CMS provides coverage for patients who have a clinical diagnosis of mild cognitive impairment (MCI) due to AD or mild AD dementia, both with confirmed presence of amyloid beta pathology consistent with AD:

1) Patient must be enrolled in Medicare
2) Patients must have a diagnosis of MCI due to AD or mild AD dementia, with documented evidence of beta-amyloid plaques in the brain **– This policy supports defining the diagnosis with documented evidence for purposes of safety and efficacy.**
3) Physician must participate in a qualifying registry* with an appropriate clinical team and follow-up care† (†Prescribing clinicians or their staff shall submit at first baseline treatment via the dedicated CMS CED data submission portal and every 6 months for up to 24 months (5 total assessments). Reference: Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease

The above conditions only apply to amyloid-targeting drugs with a traditional FDA approval, however. Under the same NCD, CMS outlined more restrictive coverage conditions for such drugs under *an accelerated approval.* To qualify for Medicare coverage, patients taking those drugs must be enrolled in randomized, controlled clinical trials conducted either through the FDA or the National Institutes of Health.

APPLICABLE HCPCS

J0175: Injection, donanemab-azbt, 2 mg [Kisunla]

Available Dosage Form: 350 mg/20 mL (17.5 mg/mL) single-dose vial

CLINICAL CRITERIA

I. INITIAL CRITERIA

Kisunla (donanemab-azbt) may be authorized when the requirements outlined in CMS National Coverage Determination 200.3 'Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (AD)' (published April 7, 2022) **AND ALL** of the following criteria are submitted with relevant clinical documentation:

A. Prescribed by, or in consultation with, a geriatrician, neurologist, or neuropsychiatrist; **AND**

B. Documented diagnosis of **ONE** of the following (TRAILBLAZER-ALZ 2):

1. Mild cognitive impairment (MCI) due to AD; **or**

2. Mild AD dementia.

AND

C. Amyloid beta deposits consistent with a diagnosis of AD are present, as confirmed by one of the following diagnostic tests. Submit copy of medical imaging results or diagnostic immunoassay: (TRAILBLAZER-ALZ 2)

1. Amyloid Positron Emission Tomography (PET), **or**

2. Cerebrospinal fluid assessment is positive for the presence of abnormal amyloid beta plaque burden.

AND

D. ONE or more of the following cognitive assessment scores at baseline indicating a diagnosis of MCI or mild AD:

1. Functional Test: Clinical Dementia Rating (CDR)

2. Cognitive Test: Mini-Mental Examination Status (MMSE); MMSE, MOCA, or other neuropsychological test

**Refer to Appendix section for additional information on Functional and Cognitive Test.*

AND

E. Baseline MRI (within the past year) does not indicate the presence of any of the following (Label; TRAILBLAZER-ALZ 2):

1. Presence of amyloid-related imaging abnormalities of edema or effusion; **or**
2. More than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter); **or**
3. A single macrohemorrhage >10 mm at the greatest diameter; **or**
4. An area of superficial siderosis; **or**
5. Evidence of vasogenic edema.

AND

F. Prescriber attestation that monitoring for Amyloid Related Imaging Abnormalities (ARIA) will be conducted via MRI as follows (Label):

   1. Prior to initiation and prior to the 2nd, 3rd, 4th, and 7th infusions; **and**

   2. Prior to the next dose if ARIA is suspected.

   **If radiographically observed ARIA occurs, treatment recommendations based on type, severity, and presence of symptoms are provided in the Kisunla Prescribing Information.*

AND

G. Member has been evaluated/screened for the presence of the following conditions and there is NO evidence of the following disease or conditions:

   1. Significant pathological findings on pre-treatment MRI; **or**

   3. History of bleeding disorder that would present a risk for ARIA-related bleeding.

AND

H. Prescriber has counseled member (or caregiver) on the following:

   1. Potential safety risks of treatment, including risks of ARIA-H and ARIA-E (Label) and based on the clinical judgement of the provider, the benefits of continuation outweigh the risks; **and**

   2. Individuals who are apolipoprotein E (ApoE) ε4 homozygotes (about 15% of people with AD) who are treated with Kisunla are more likely to develop ARIA, including symptomatic, serious, and severe radiographic ARIA, compared to heterozygotes and non-carriers (Label); **and**

   3. Member on anticoagulants: Safety risks for ARIA have been discussed; caution should be exercised when considering the use of Kisunla in patients on anticoagulants or patients with findings on MRI that are suggestive of Cerebral Amyloid Angiopathy; **and**

   4. Members with a bleeding disorder that is not under adequate control: Kisunla therapy is not started until the bleeding disorder has been controlled; **and**

      **Bleeding disorder status is assessed using platelet count (<50,000) or international normalized ratio [INR] (>1.5) for patients who are not on anticoagulants such as warfarin.*

   5. Members on anticoagulant therapy: Anticoagulant status optimized and be on a stable dose for 4 weeks before initiating Kisunla therapy.

AND

I. Member / patient will be included in CMS-approved coverage with evidence development (CED) registry (registry number, CED submission date, and submission number should be provided, if applicable).

II. REAUTHORIZATION / CONTINUATION OF THERAPY CRITERIA

Kisunla (donanemab-azbt) may be authorized for continuation of therapy when initial criteria have been met AND there is documentation of beneficial response from previous course of treatment:

A. Absence of unacceptable toxicity from the drug (e.g., intracerebral macro hemorrhage, etc.); **AND**

B. Member continues to meet the initial therapy criteria (outlined in section A above) AND has **not** progressed to *moderate or severe AD*, documented by evidence of the following:
   1. No symptomatic moderate to severe ARIA-E; **and**
   2. No moderate to severe ARIA-E based on MRI; **and**
   3. No symptomatic ARIA-H; **and**
   4. No moderate to severe ARIA-H based on MRI.

C. Member has received a brain MRI at baseline and before the second, third, fourth, and seventh infusions as appropriate.

**Prescribers may consider discontinuation of treatment based on the reduction of amyloid plaques to minimal levels on amyloid PET imaging. In the TRAILBLAZER-ALZ 2 study, 17% of patients completed treatment at 6 months, 47% completed treatment at 12 months, and 69% completed treatment at 18 months.*

III. EXCLUSIONS

Kisunla (donanemab-azbt) may not be authorized for the following (TRAILBLAZER-ALZ 2):

A. Any medical or neurological condition, other than AD, which might be a contributing cause of the individual's cognitive impairment (TRAILBLAZER-ALZ 2); OR
B. Contraindications to brain MRI scanning (such as non-MRI compatible pacemaker/defibrillator or other implants) (TRAILBLAZER-ALZ 2); OR
C. Evidence of other clinically significant lesions on brain MRI that indicate another cause of the individual's cognitive impairment (TRAILBLAZER-ALZ 2); OR
D. Uncontrolled bleeding disorder, including those with a platelet count <50,000; OR
E. International normalized ratio [INR] >1.5 (TRAILBLAZER-ALZ 2); OR
F. Any uncontrolled immunological disease or immunological disease requiring treatment with immunoglobulins, systemic monoclonal antibodies (or derivatives of monoclonal antibodies), systemic immunosuppressants, or plasmapheresis.

STEP THERAPY

Step therapy criteria do not apply for members who are currently being treated with the requested medications. Step therapy is only applied for members that are new to therapy (have not received the requested drug in the last 365 days.

No Step Therapy required.

DOSAGE AND AUTHORIZATION TIMEFRAMES

1. Recommended Dose: The recommended dosage of Kisunla is 700mg IV every 4 weeks for 3 doses, then 1400mg IV every 4 weeks. The IV infusion is given over approximately 30 minutes.

2. Quantity Limit: FOUR (4) vials (80 mL) per 4 weeks

3. Authorization Period
   a. Initial authorization: May be authorized for up to 6 months.
   b. Continuation of treatment authorization: May be authorized for up to 6 months.

DRUG INFORMATION

PHARMACOLOGIC CATEGORY: Anti-Amyloid Monoclonal Antibody; Immune Globulin; Monoclonal Antibody

ROUTE OF ADMINISTRATION: Intravenous Infusion

FDA-APPROVED INDICATIONS:

Alzheimer disease (AD): Treatment of AD; to be initiated in patients with mild cognitive impairment or mild dementia stage of disease.

COMPENDIAL APPROVED OFF-LABELED USES: None

Off-Label / Investigational Uses: Requests for off-label uses with a paucity of clinical evidence or uses that are not generally accepted by the medical community (such as professional guidelines or consensus), CMS- recognized compendia, or peer-reviewed literature is considered investigational and will not be authorized due to insufficient evidence of overall therapeutic value of safety and efficacy.

BOXED WARNING
The Kisunla label includes boxed warnings for risk of **Amyloid Related Imaging Abnormalities (ARIA)** with possible serious and life-threatening events occurring. Kisunla can cause amyloid related imaging abnormalities -edema (ARIA-E) and -hemosiderin deposition (ARIA-H). ARIA incidence and timing vary among treatments. ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events rarely can occur. Serious intracerebral hemorrhages >1 cm, some fatal, have been observed. Because ARIA-E can cause focal neurologic deficits that can mimic ischemic stroke, treating clinicians should consider whether such symptoms could be due to ARIA-E before giving thrombolytic therapy in a patient being treated.

Patients who are **apolipoprotein E (ApoE) homozygotes** have a higher incidence of ARIA, including symptomatic and serious ARIA, compared to heterozygotes and noncarriers. Testing for ApoE ε4 status should be performed prior to beginning treatment to inform the risk of developing ARIA. Inform patients that if genotype testing is not performed, they can still be treated with; however, it cannot be determined if they are ApoE ε4 homozygotes and at higher risk for ARIA.

During treatment, patients should be monitored for ARIA; dosing interruptions may be necessary for patients with ARIA-E and ARIA-H. Consider the benefit of donanemab for the treatment of AD and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment with donanemab.

CONTRAINDICATIONS: Serious hypersensitivity (e.g., anaphylaxis) to donanemab or any component of the formulation.

OTHER CONSIDERATIONS
Monitoring for ARIA:

- PET or lumbar puncture to confirm presence of amyloid beta pathology (prior to initiation).
- Apolipoprotein E ε4 (ApoE ε4) status testing (prior to initiation).
- Brain MRI: Prior to initiation; prior to 2nd, 3rd, 4th, and 7th infusions; periodically, as appropriate in the setting of ARIA (e.g., 2 to 4 months following identification of ARIA]) or if symptoms of ARIA develop.
- Monitor closely for clinical and MRI changes; monitor for symptoms suggestive of ARIA (e.g., headache, altered mental status, visual changes, dizziness, nausea, gait difficulty, focal neurologic deficits, seizure).
- Provider-enrolled patient registry: CMS requires participation in a CMS-facilitated registry as part of coverage requirements for Kisunla.

CLINICAL SUMMARY / APPENDIX

Kisunla (donanemab-azbt) is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against insoluble N-truncated pyroglutamate amyloid beta. Donanemab reduces amyloid beta plaques, the accumulation of which is a defining pathophysiological feature of Alzheimer disease (AD).

FDA's approval was based on a double-blind, placebo-controlled, parallel-group study evaluating the efficacy of Kisunla in slowing cognitive decline in participants with varying levels of tau protein in the brain. Tau is a protein that helps to stabilize the neurons in the brain. The TRAILBLAZER-ALZ 2 Phase 3, double-blind, placebo-controlled study (**NCT04437511**) evaluated the safety and efficacy of donanemab in 1,736 participants with early symptomatic AD (MCI or mild dementia due to AD) with the presence of confirmed AD neuropathology. The trial enrolled participants aged 60 to 85 years), across 8 countries, selected based on cognitive assessments in conjunction with evidence of AD pathology. The Phase 3 TRAILBLAZER-ALZ 2 study results were **published** in the *Journal of the American Medical Association* (JAMA).

Patients with early symptomatic AD with amyloid and low/medium or high tau pathology were randomly assigned to receive donanemab (700mg IV every 4 weeks for the first 3 doses, and then 1400mg every 4 weeks (n=860) or placebo (n=876) for a total of up to 72 weeks. Trial participants were analyzed over 18 months in two groupings: one group who was less advanced in their disease (those with low to medium levels of tau protein) and the overall population, which also included participants with high tau levels.

Amyloid positron emission tomography (PET) levels were measured at weeks 24, 52, and 76. If the amyloid plaque level was less than 11 Centiloids on a single PET scan or 11 to less than 25 Centiloids on 2 consecutive PET scans, the patient was eligible to be switched to placebo.

The primary study outcome was the change in integrated Alzheimer Disease Rating Scale (iARDS) score—which measures thinking, memory, and daily functioning—from baseline to 76 weeks (total score ranges from 0 to 144 with lower scores indicating worse cognitive and functional performance). Findings showed patients treated with donanemab demonstrated a statistically significant reduction in clinical decline on iADRS compared with placebo at week 76 in the combined population (2.92, P <.0001) and the low/medium tau population (3.25, P <.0001). Compared with placebo, statistically significant differences were also observed in the combined population treated with donanemab on the Clinical Dementia Rating-Sum of Boxes (-0.70 [29%]; P <.0001), the Alzheimer Disease Assessment Scale – 13-item Cognitive Subscale (-1.33 [20%]; P =.0006), and the Alzheimer Disease Cooperative Study – instrumental Activities of Daily Living subscale (1.70 [28%]; P =.0001).

Summary of Study Findings

- Patients who were the least advanced in the disease experienced the strongest results with Kisunla.
- Patients who were the least advanced in the disease experienced the strongest results with Kisunla. Trial participants were analyzed over 18 months in two groupings: one group who was less advanced in their disease (those with low to medium levels of tau protein) and the overall population, which also included participants with high tau levels. Treatment with Kisunla significantly slowed clinical decline in both groups. Those individuals treated with Kisunla who were less advanced in their disease showed a significant slowing of decline of 35% compared with placebo on the iADRS, which measures memory, thinking, and daily functioning. In the overall population, the response to treatment was also statistically significant using the iADRS at 22%. Among the two groups analyzed, participants treated with Kisunla had up to a 39% lower risk of progressing to the next clinical stage of disease than those taking placebo.
- The study monitored amyloid plaque levels using PET scans throughout the treatment period. Results showed substantial reductions in amyloid plaques over time among patients receiving Kisunla, with reductions of 61% at six months, 80% at 12 months, and 84% at 18 months compared to baseline levels.
- In the overall population of people receiving Kisunla, 17% completed treatment at 6 months, 47% at 12 months, and 69% at 18 months based on an assessment of amyloid levels via an amyloid PET scan.

The most common side effects of Kisunla were ARIA and headache. The most common ARIA is a temporary swelling in an area or areas of the brain (ARIA-E) or a small brain bleed "microhemorrhages" or a

more severe brain bleed, “superficial siderosis” (ARIA-H).

Additional studies following FDA approval are necessary to ensure the safety and long-term effectiveness of all anti-amyloid therapies. As a result, CMS has mandated that patients receiving anti-amyloid therapy must have their data recorded in a registry facilitated by CMS. There are still uncertainties regarding whether the clinical benefit observed in the anti-amyloid therapy clinical trial translates to measurable changes in the lives of patients with AD. Ongoing debates surround the effectiveness of clearing amyloid as a treatment for AD symptoms.

Studies of donanemab are ongoing:

- TRAILBLAZER-ALZ 3 is focused on preventing symptomatic AD in patients with preclinical disease.
- TRAILBLAZER-ALZ 5 is a registration trial for early symptomatic AD, enrolling patients in China and Korea.
- TRAILBLAZER-ALZ 6 is focused on expanding the understanding of ARIA through novel MRI sequences, blood-based biomarkers, and different dosing regimens of donanemab”

Definitions

Amyloid Related Imaging Abnormalities (ARIA): Abnormalities observed in the brain on magnetic resonance imaging (MRI).

- ARIA with edema (ARIA-E): findings consistent with brain edema or sulcal effusions
- ARIA with hemorrhage (ARIA-H): findings consistent with microhemorrhage and superficial siderosis

Clinical Dementia Rating (CDR) scale: Measure used to stage dementia in the clinical and research setting, comprising of 75 items related to cognition and function.

Global Score (CDR-GS, or plainly, CDR): Calculated score that provides an overall rating of dementia severity using six areas – Memory*, Orientation, Judgment/Problem Solving, Community Affairs, Home/Hobbies, and Personal Care.

- 0 = no dementia/normal
- **0.5 = questionable cognitive impairment/very mild dementia**
- **1 = mild cognitive impairment/mild dementia**
- 2 = moderate dementia
- 3 = severe dementia

*CDR Memory (M) Box Score: Considered the primary category within the CDR-GS rating tool. All other categories are secondary. Final CDR-GS score is based on an algorithm with the memory box score playing a significant role in the calculation.

Sum of Boxes Score (CDR-SB): Detailed quantitative general index across the six categories.

- 0: no dementia/normal
- 0.5 – 4.0: questionable cognitive impairment
- 0.5 – 2.0: questionable impairment
- 2.5 – 4.0: very mild dementia
- 4.5 – 9.0: mild dementia
- 9.5 – 15.5: moderate dementia
- 16.0 – 18.0: severe dementia

Mild cognitive impairment (MCI) related to AD: Stage categorized by symptoms of memory and/or other thinking problems that are not normal for the individual’s age and education, but that usually do not interfere with his or her independence. Sometimes referred to as the symptomatic predementia phase of AD.

Mini Mental State Examination (MMSE): An 11-question tool used to assess mental status that tests five areas of cognitive function – Orientation, Registration, Attention/Calculation, Recall, and Language. Scale is a range from 0 to 30 with 0 being severe dementia and 30 is no dementia. It is scored on a 30-point scale with scores <24 typically regarded as abnormal and indicative of cognitive impairment. Of note, age, education, and race/ethnicity have been shown to affect MMSE scores and should be considered when evaluating an

individual patient.

Montreal Cognitive Assessment (MoCA): The MoCA includes a broader range of cognitive domains, particularly executive abilities, and is able to detect more subtle cognitive deficits that characterize MCI. It evaluates delayed word recall, visuospatial/executive function, language, attention/concentration, and orientation. The MoCA is also scored on a 30-point scale, with scores of 18-25 suggestive of MCI. The cut-off score of 18 is usually considered to separate MCI from Alzheimer's disease, though there is overlap in the scores as AD is determined by the presence of cognitive impairment as well as the loss of functional independence.

REFERENCES

Government Agency

Centers for Medicare and Medicaid Services (CMS). Medicare coverage database: National coverage determination (NCD) (search: Leqembi, lecanemab). Available from CMS: Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (AD)

Prescribing Information

Kisunla. Prescribing Information. Eli Lilly; 2024. Accessed July 2, 2024.

Clinical Trials

NCT04437511 (TRAILBLAZER-ALZ 2)
NCT04640077 (TRAILBLAZER-EXT)
NCT05026866 (TRAILBLAZER-ALZ 3)
NCT05508789 (TRAILBLAZER-ALZ 5)
NCT05738486 (TRAILBLAZER-ALZ 6)

Peer Reviewed Literature, Guidelines

Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J, Wessels AM, Shcherbinin S, Wang H, Monkul Nery ES, et al. Donanemab in early symptomatic Alzheimer disease: The TRAILBLAZER-ALZ 2 randomized clinical trial. JAMA. 2023;330(6):512-527. doi: 10.1001/jama.2023.13239.

IMPORTANT REMINDER

This Medicare Part B Step Therapy Medical Necessity Guideline is provided for informational purposes only and neither constitutes nor replaces professional medical advice. Physicians, hospitals, and other providers are expected to administer or use drugs/biologicals in the most effective and clinically appropriate manner. Treating physicians and other health care providers are solely responsible for all medical care decisions. In accordance with the member's Evidence of Coverage (EOC), every benefit plan has its own coverage provisions, limitations, and exclusions. In the event of a conflict between this policy and the member's EOC, the member's EOC provisions will take precedence.

Aspire Health Plan adheres to Medicare guidelines, including National Coverage Determination (NCD), Local Coverage Determinations (LCDs), Local Coverage Articles (LCAs), and other relevant Medicare manuals established by CMS. Compliance with these guidelines is required when applicable. Refer to the CMS website at http://www.cms.hhs.gov. For the most up-to-date Medicare policies and coverage, please search the Medicare Coverage Database. All LCDS are the same for each state within a Jurisdiction. Medicare Part B Administrative Contractor (MAC) for CA [Jurisdiction E (1)]: Active LCDs - JE Part B – Noridian (noridianmedicare.com). In the event of a discrepancy between this policy and the Medicare NCD or LCD, the Medicare NCD/LCD will govern.

This policy is utilized by Aspire Health Plan to determine coverage in the absence of applicable CMS Medicare guidelines. Please refer to the links provided in the References section below to access the Medicare source materials that were used for developing this resource document. This document does not serve as a substitute for the official Medicare source materials that provide detailed information on Medicare coverage requirements. In the event of a conflict between this document and Medicare source materials, the Medicare source materials will take precedence.

The inclusion of a code in this policy does not imply that the health service it describes is covered or not covered. Benefit coverage for health services is determined by the member-specific plan document and applicable laws that may mandate coverage for a particular service. Inclusion of a code does not imply or guarantee reimbursement or payment of a claim. Other Policies and Standards may also apply. Providers are expected to retain or have access to the necessary documentation when requested in order to support coverage.

POLICY HISTORY

Committee Date	Summary of Changes
08/27/2024	New Policy (effective 12/15/2024)