Kisunla (donanemab-azbt)

Summary

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that can lead to dementia. Alzheimer's dementia is characterized by cognitive decline, memory impairment, and functional disability. Treatment goals for dementia include improving cognitive function and overall quality of life. Alzheimer's disease is the most common cause of dementia, affecting millions of people worldwide.

Alzheimer's dementia is often treated with acetylcholinesterase inhibitors (AChEIs), such as donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne), as first-line therapy for those with mild, moderate or severe dementia. Alternative therapies include N-methyl-D-aspartate (NMDA) receptor antagonists such as memantine (Namenda) for moderate-to-severe dementia - which can be used as monotherapy or combined with AChEIs. Additionally, newer amyloid-targeting therapies, such as Leqembi (lecanemab) and Kisulna (donanemab), are indicated for initiation in those with mild cognitive impairment or mild dementia.

Kisunla (donanemab-azbt) is a monoclonal antibody that targets amyloid beta plaques in the brain and is approved by the FDA for treatment of early Alzheimer's disease (AD). While clinical trials have shown some potential benefits in slowing cognitive decline, the evidence is limited and the clinical meaningfulness of the observed effects remains uncertain. Additionally, monoclonal antibodies directed

against aggregated forms of beta amyloid, like Kisunla (donanemab-azbt,) are associated with risks of amyloid-related imaging abnormalities (ARIA) that can be serious. ARIA is usually asymptomatic, although serious and life-threatening events can occur, which can be fatal. Serious intracerebral hemorrhages greater than 1 cm have occurred in those treated with this class of medications. ARIA-E can cause focal neurologic deficits that can mimic ischemic stroke. Given the limited evidence of clinically meaningful benefit and potential risks, Kisunla (donanemab-azbt) is considered not medically necessary for the treatment of Alzheimer's disease at this time.

Definitions

"Alzheimer's disease (AD)" is a progressive neurodegenerative disorder characterized by cognitive decline, memory loss, and functional impairment.

"Mild cognitive impairment (MCI)" refers to an early stage of cognitive decline that may progress to dementia.

"Amyloid beta (Aβ)" are protein fragments that accumulate to form plaques in the brains of Alzheimer's patients.

"Amyloid-related imaging abnormalities (ARIA)" refers to brain swelling or bleeding that can occur with anti-amyloid therapies. ARIA can be broken down into subtypes: ARIA-E (edema/effusion), and ARIA-H (microhemorrhage and superficial siderosis).

Policy Statement on Kisunla (donanemab-azbt) for Alzheimer's Disease Efficacy Information

The use of Kisunla (donanemab-azbt) is considered not medically necessary for the treatment of Alzheimer's disease or any other indication, as the available evidence is insufficient to demonstrate clinically meaningful benefit that outweighs potential risks.

- The phase III TRAILBLAZER-ALZ 2 trial showed Kisunla (donanemab-azbt) slowed cognitive decline by 35.1% in patients with low/medium tau and by 22.3% in the overall population over 76 weeks, as measured by the integrated Alzheimer's Disease Rating Scale (iADRS).
- Secondary outcomes showed modest benefits on measures like the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) and activities of daily living.
- Kisunla (donanemab-azbt) substantially reduced amyloid plaque levels but did not significantly affect tau protein levels.
- The earlier phase II TRAILBLAZER-ALZ trial showed a modest 3.2 point difference on the iADRS but failed to meet secondary clinical endpoints.
- The phase III TRAILBLAZER-ALZ 4 trial assessed Kisunla (donanemab-azbt) against a previously approved amyloid-targeting monoclonal antibody, aducanumab (aducanumab has since been removed from the US market). Amyloid plaque clearance was significantly greater at 6, 12, and 18 months in the Kisunla (donanemab-azbt) group compared to the aducanumab-treated arm.

Rates of ARIA were also significantly lower in the Kisunla (donanemab-azbt) arm compared to the aducanumab-treated arm (29.6% versus 40.6% for all ARIA subtypes at 18 months). This study did not assess individual-oriented and clinical outcomes related to cognitive function, as it was open-label.

- A secondary analysis of the TRAILBLAZER-ALZ, TRAILBLAZER-ALZ 2 studies, adn an open-label addendum. In a total of 3030 participants, both ARIA edema/effusion (ARIA-E), and ARIA-microhemorrhages and hemosiderin (ARIA-H) were signficant higher in the Kisunla (donanemab-azbt) group compared to placebo (24.4% and 31.3% versus 1.9% and 13.0%, respectively). Rates of serious ARIA-E (1.5%), and symptomatic ARIA-E (5.8%) were low. The most common risk factors for higher rates of ARIA-E were: APOE ε4 allele number, greater number of microhemorrhages, presence of cortical superficial siderosis, higher amyloid plaque, and elevated mean arterial pressure. Antihypertensive use was associated with a lower risk of ARIA-E.

The use of Kisunla (donanemab-azbt) is associated with significant safety concerns that must be carefully weighed against its modest efficacy. Key risks include:

- Amyloid-Related Imaging Abnormalities (ARIA):
    - ARIA occurred in 36% of patients treated with donanemab compared to 14% on placebo.
    - ARIA-E (edema) occurred in 24% of donanemab patients vs 2% on placebo.
    - ARIA-H (microhemorrhage) occurred in 25% vs 13% on placebo.
    - Symptomatic ARIA occurred in 6% of donanemab patients.
    - Severe ARIA-E occurred in 2%, severe ARIA-H microhemorrhage in 5%, and severe ARIA-H superficial siderosis in 5% of patients.
- Intracerebral Hemorrhage:
    - Intracerebral hemorrhage >1 cm occurred in 0.5% (4/853) of donanemab patients vs 0.2% (2/874) on placebo.
    - Three patients died after developing serious ARIA.
- Increased Risk in ApoE ε4 Homozygotes:
    - ARIA incidence was higher in ApoE ε4 homozygotes (55%) compared to heterozygotes (36%) and noncarriers (25%).
    - Severe ARIA rates were also higher in homozygotes.
- Other Adverse Effects:
    - Infusion-related reactions occurred in 9% of donanemab patients vs 0.5% on placebo.
    - Hypersensitivity reactions occurred in 3% of donanemab patients vs 0.7% on placebo.
- Testing for ApoE ε4 status is recommended before initiating treatment.
- The prescribing information contains a boxed warning about the risk of ARIA.
    - Baseline brain MRI and periodic MRIs are required to monitor for ARIA.
    - Enhanced clinical vigilance for ARIA is recommended during the first 24 weeks of treatment.

Medical Necessity Criteria for Kisunla (donanemab-azbt) for Alzheimer's Disease

Kisunla (donanemab-azbt) is considered not medically necessary for any indication, including for the treatment of Alzheimer's disease.

Experimental or Investigational / Not Medically Necessary

Kisunla (donanemab-azbt) is considered experimental, investigational, and not medically necessary for the treatment of Alzheimer's disease or any other indication for the following reasons:

1. While clinical trials have shown some potential for slowing cognitive decline, the magnitude of benefit is modest and of uncertain clinical significance.
2. Kisunla (donanemab-azbt) is associated with risks of ARIA, which can be serious and potentially life-threatening in some cases.
3. There is insufficient evidence that the potential benefits of Kisunla (donanemab-azbt) outweigh its risks in real-world clinical practice outside of clinical trials.
4. Professional guidelines have not yet recommended routine use of Kisunla (donanemab-azbt) for Alzheimer's disease management. In March of 2025, the European Medicines Agency Committee recommended not granting marketing authorization ot Kisunla (donanemab-azbt), however in July of 2025, after a re-examination procedure, the Committee changed positing and will now be recommended the product be allowed marketing authorization. The United Kingdom's National Institute for Healthcare Excellence (NICE), is pending a guidance document for Kisunla (donanemab-azbt). In June 2025, the NICE final draft guidance found there was still too little benefit for both Kisunla (donanemab-azbt) and Leqembi (lecanemab) "to justify the cost to the NHS [National Health System]" - the final draft has not yet been posted.

Given these limitations in the current evidence, Kisunla (donanemab-azbt) is considered not medically necessary for the treatment of Alzheimer's disease or any other indication at this time. The Plan will continue to review emerging evidence on Kisunla (donanemab-azbt) and may reevaluate this policy as new data become available.

Applicable Billing Codes (HCPCS/CPT Codes)

Service(s) name	
CPT/HCPCS Codes considered experimental or investigational or not considered medically necessary:	
Code	*Description*
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour

J0175	Injection, donanemab-azbt, 2 mg
ICD-10 Codes considered experimental or investigational or not considered medically necessary:	
Code	*Description*
G30.0	Alzheimer'S Disease With Early Onset
G30.1	Alzheimer'S Disease With Late Onset
G30.8	Other Alzheimer'S Disease
G30.9	Alzheimer'S Disease, Unspecified
Z00.6	Encounter For Examination For Normal Comparison And Control In Clinical Research Program

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Clinical Guideline Revision / History Information

Original Date: 09/18/2024 Reviewed/Revised: 01/01/2026