Policy Number	**RX501.177**
Policy Effective Date	**5/7/2026**

Donanemab-azbt

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of care developed by: nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association, New England Journal of Medicine, and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated, and coverage is not required for non-formulary drugs.

EXCEPTION: For **Illinois** only: Effective July 1, 2025, PA 103-0975, 5ILCS 375/6.11D, SB3318 Alzheimer Treatment, requires the State Employees Group Insurance Program to provide coverage for all medically necessary FDA-approved treatments or medications prescribed to slow the progression of Alzheimer's Disease or another related dementia, as determined by a physician licensed to practice medicine in all its branches. Coverage for all FDA-approved treatments or medications prescribed to slow the progression of Alzheimer's Disease or another related dementia shall not be subject to step therapy. Any diagnostic testing necessary for a physician to determine appropriate use of these treatments or medications shall be covered by the State Employees Group Insurance Program.

Coverage

Donanemab-azbt (Kisunla) **may be considered medically necessary** for the treatment of Alzheimer's Disease (AD) when **ALL** the following criteria are met:

- Individual is aged 50 years or older; AND
- Individual has mild cognitive impairment due to AD or mild AD dementia; AND
- Individual has positive amyloid load as indicated by one of the following:
  - Positron emission tomography assessment of imaging agent uptake into brain; or
  - Cerebrospinal fluid assessment of amyloid β (Aβ1-42); AND
- Individual has a baseline brain magnetic resonance imaging (MRI) prior to initiating treatment; AND

- Individual must have one of the following scores at baseline on any of the following assessment tools:
  - Clinical Dementia Rating-Global Score of 0.5 or 1; or
  - Mini-Mental Status Examination score of 22-28.

Donanemab-azbt (Kisunla) **is considered experimental, investigational and/or unproven** for all other non-Food and Drug Administration approved indications.

Policy Guidelines

None.

Description

Alzheimer's Disease
Alzheimer's disease is a fatal neurodegenerative disease that causes progressive loss in memory, language, and thinking, with the eventual loss of ability to perform social and functional activities in daily life. Survival after a diagnosis of dementia due to AD generally ranges between 4 and 8 years; however, life expectancy can be influenced by other factors, such as comorbid medical conditions. It is estimated that 7.2 million Americans aged 65 and older are currently living with AD dementia, and the number could reach 13.8 million by 2060. (2)

Pathophysiology
Brain amyloid deposition is a marker of AD pathology. The accumulation of the protein fragment beta-amyloid into clumps (called beta-amyloid plaques) outside neurons and the accumulation of an abnormal form of the protein tau (called tau tangles) inside neurons are two of several brain changes associated with Alzheimer's disease. Beta-amyloid and tau accumulation is followed by damage to and destruction of neurons (called neurodegeneration) and other brain cells. Neurodegeneration, along with beta-amyloid and tau accumulation, is a key feature of Alzheimer's disease. These changes in the brain result in widespread neurodegeneration and cell death and ultimately cause the clinical signs and symptoms of dementia. (3, 4)

Salient known risk factors for AD are older age, genetics, and family history. Of these, increasing age has the largest known impact on risk of developing AD. While several genes have been found to increase the risk of AD, the ε4 allele of the apolipoprotein E gene is the strongest known genetic risk factor. (5, 6) Having a single copy of the gene is associated with a 2- to 3-fold increase in developing AD while 2 copies of the gene may increase risk of AD by as much as 15 times. (7) Approximately two-thirds of pathology-confirmed AD cases are ε4 positive (homozygous or heterozygous), compared with about 15% to 20% of the general population. (6) Autosomal dominant genetic mutations are estimated to account

for less than 1% of AD cases. (8) The pathophysiological changes and clinical manifestations of AD are progressive and occur along a continuum, and accumulation of amyloid beta may begin 20 years or more before symptoms arise. (9)

The National Institute on Aging-Alzheimer's Association 2011 guidelines set clinical criteria for mild cognitive impairment and dementia. (11, 12) Mild cognitive impairment lies between the cognitive changes of normal aging and dementia. Individuals with MCI are at increased risk of developing dementia (whether from AD or another etiology), but many do not progress to dementia, and some get better. Dementia is a syndrome involving cognitive and behavioral impairment in an otherwise alert patient, due to a number of neurological diseases, alone or combined. It is not a specific cause or disease process itself. The impairment must involve a minimum of 2 domains (memory, reasoning, visuospatial abilities, language or personality behaviors), impact daily functioning, represent a decline from previous levels of functioning, not be explainable by delirium (a temporary state of mental confusion and fluctuating consciousness from various causes) or a major psychiatric disorder, and be objectively documented by a "bedside" mental status exam (e.g., the mini-mental status exam) or neuropsychological testing. (12) These guidelines describe core clinical criteria for "all-cause" dementia and "probable AD" dementia. Briefly, "probable AD" dementia must first meet the criteria for "all-cause" dementia. Additionally, there must be: (a) insidious onset; (b) documented worsening of cognition; (c) exclusion of major concomitant cerebrovascular disease (as most individuals with AD have some level of this as well); and (d) exclusion of alternative diagnoses (e.g., dementia with Lewy bodies, behavioral variant frontotemporal dementia, progressive aphasia, or other neurological disease associated with dementia). A clinical diagnosis of "possible AD" dementia would meet the criteria for "probable AD" with the exception of having an "atypical course" (e.g., sudden rather than insidious onset) or an "etiologically mixed presentation."

In 2024, NIA-AA updated their "numeric clinical staging scheme" (Table 1) that avoids traditional syndromal labels and is applicable for only those in the Alzheimer continuum. (13) This staging scheme reflects the sequential evolution of AD from an initial stage characterized by the appearance of abnormal AD biomarkers in asymptomatic individuals. The biological definition of AD is consistent with the distinction between a disease and an illness. A disease is a pathogenic condition, while the term illness denotes signs and symptoms that result from the disease. For individuals with biologically confirmed AD, we believe that numeric staging provides a clarifying framework for categorizing the clinical continuum of AD. The term prodromal AD has been used to denote individuals with abnormal AD biomarkers who have clinically evident impairment that falls short of dementia. As biomarker abnormalities progress, the earliest subtle symptoms become detectable. Further progression of biomarker abnormalities is accompanied by progressive worsening of cognitive symptoms, culminating in dementia. These criteria are not intended to provide step-by-step clinical practice guidelines for clinical workflow or specific treatment protocols. Instead, they serve as general principles to inform diagnosis and staging of AD that reflect current science. This numeric staging scheme is very similar to the

system for staging AD outlined in the Food and Drug Administration (FDA) guidance for conduct of clinical trials in early AD. (10)

Current Treatment

Current treatment goals for patients with AD are often directed to maintain quality of life, treat cognitive symptoms, and manage behavioral and psychological symptoms of dementia. Treatment remains largely supportive, including creation and implementation of individualized dementia care plans, caregiver education and support, care navigation, care coordination, and referral to community-based organizations for services (e.g., adult day care, caregiver training). (14) Non-pharmacologic treatments include physical activity (15, 16) as well as behavioral strategies to ameliorate neuropsychiatric symptoms (e.g., agitation, delusions, disinhibition) and problem behaviors (e.g., resistance to care, hoarding, obsessive-compulsive behaviors). (17) Currently, FDA-approved drugs for AD include cholinesterase inhibitors, donepezil, rivastigmine, and galantamine, and the N-methyl-D-aspartate antagonist, memantine. Cholinesterase inhibitors are indicated in mild, moderate, and severe AD, while memantine is approved for moderate-to-severe AD. These drugs, either alone or in combination, focus on managing cognitive and functional symptoms of the disease and have not been shown to alter disease trajectory. The evidence for efficacy is limited and these agents are associated with significant side effects. (18, 19)

Table 1. National Institute on Aging-Alzheimer's Association Numerical Clinical Staging for Individuals in the Alzheimer Continuum (13)

Stage	Severity	Clinical Features
Stage 0	Asymptomatic, deterministic gene[a]	• No evidence of clinical change. Biomarkers in normal range.
Stage 1	Asymptomatic, biomarker evidence only	• Performance within expected range on objective cognitive tests. • No evidence of recent cognitive decline or new symptoms.
Stage 2	Transitional decline: mild detectable change, but minimal impact on daily function	• Normal performance within expected range on objective cognitive tests. • Decline from previous level of cognitive or neurobehavioral function that represents a change from individual baseline within the past 1 to 3 years and has been persistent for at least 6 months. • May be documented by evidence of subtle decline on longitudinal cognitive testing, which may involve memory or other cognitive domains but performance still within normal range. • May be documented through subjective report of cognitive decline.

		• May be documented with recent onset change in mood, anxiety, motivation not explained by life events. • Remains fully independent with no or minimal functional impact on activities of daily living (ADLs).
Stage 3	Cognitive impairment with early functional impact	• Performance in the impaired/abnormal range on objective cognitive tests. • Evidence of decline from baseline, documented by the individual's report or by an observer's (e.g., study partner) report or by change on longitudinal cognitive testing or neurobehavioral assessments. • Performs daily life activities independently, but cognitive difficulty may result in detectable functional impact on complex ADLs (i.e., may take more time or be less efficient but still can complete—either self-reported or corroborated by an observer).
Stage 4	Dementia with mild functional impairment	• Progressive cognitive and mild functional impairment on instrumental ADLs, with independence in basic ADLs.
Stage 5	Dementia with moderate functional impairment	• Progressive cognitive and moderate functional impairment on basic ADLs requiring assistance.
Stage 6	Dementia with severe functional impairment	• Progressive cognitive and functional impairment, and complete dependence for basic ADLs.

[a] Individuals with Down syndrome may not be fully independent even in stage 0 because of underlying intellectual disability. In these individuals, decline in functional independence from baseline may be a more appropriate indicator of stage.

Donanemab-azbt (Kisunla)
Donanemab-azbt is a humanized immunoglobulin gamma 1 monoclonal antibody directed against insoluble N-truncated pyroglutamate amyloid beta. Donanemab-azbt reduces amyloid beta plaques. (1)

Monoclonal antibodies directed against aggregated forms of beta amyloid, including Kisunla, can cause amyloid related imaging abnormalities, characterized as ARIA with edema, which can be observed on MRI as brain edema or sulcal effusions, and ARIA with hemosiderin deposition, which includes microhemorrhage and superficial siderosis. ARIA can occur spontaneously in patients with Alzheimer's disease, particularly in patients with MRI findings suggestive of cerebral amyloid angiopathy, such as pretreatment microhemorrhage or superficial siderosis. ARIA-H associated with monoclonal antibodies

directed against aggregated forms of beta amyloid generally occurs in association with an occurrence of ARIA-E. ARIA-H of any cause and ARIA-E can occur together. (1)

ARIA usually occurs early in treatment and is usually asymptomatic, although serious and life-threatening events, including seizure and status epilepticus, rarely can occur. When present, reported symptoms associated with ARIA may include, but are not limited to, headache, confusion, visual changes, dizziness, nausea, and gait difficulty. Focal neurologic deficits may also occur. Symptoms associated with ARIA usually resolve over time. In addition to ARIA, intracerebral hemorrhages greater than 1 cm in diameter have occurred in patients treated with Kisunla. (1)

Regulatory Status
In 2024, the U.S. Food and Drug Administration approved donanemab-azbt (Kisunla, Eli Lilly & Co.) for the treatment of Alzheimer's disease. 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 the clinical trials. (1)

Rationale

This policy is based on the U.S. Food and Drug Administration labeled indications for donanemab-azbt (Kisunla) as well as specialty society recommendations and guidelines.

Donanemab-azbt (Kisunla) (1)
Study 1
The efficacy of donanemab-azbt (Kisunla) was evaluated in a double-blind, placebo-controlled, parallel-group study (Study 1, NCT04437511) in patients with Alzheimer's disease (patients with confirmed presence of amyloid pathology and mild cognitive impairment or mild dementia stage of disease, consistent with Stage 3 and Stage 4 Alzheimer's disease). Patients were enrolled with a Mini-Mental State Examination score of ≥20 and ≤28 and had a progressive change in memory function for at least 6 months. Patients were included in the study based on visual assessment of tau positron emission tomography (PET) imaging with flortaucipir and standardized uptake value ratio. Patients were enrolled with or without concomitant approved therapies (cholinesterase inhibitors and the N-methyl-D-aspartate antagonist, memantine) for Alzheimer's disease. Patients could enroll in an optional, long-term extension.

In Study 1, 1736 patients were randomized 1:1 to receive 700 mg of Kisunla every 4 weeks for the first 3 doses, and then 1400 mg every 4 weeks (N = 860) or placebo (N = 876) for a total of up to 72 weeks. The treatment was switched to placebo based on amyloid PET levels measured at Week 24, Week 52, and Week 76. If the amyloid plaque level was <11 Centiloids on a single PET scan or 11 to <25 Centiloids on 2 consecutive PET scans, the patient was eligible to be switched to placebo.

Additionally, dose adjustments were allowed for treatment-emergent ARIA or symptoms that then showed ARIA-E or ARIA-H on MRI.

At baseline, mean age was 73 years, with a range of 59 to 86 years. Of the total number of patients randomized, 68% had low/medium tau level and 32% had high tau level; 71% were apolipoprotein E ε4 (ApoE ε4) carriers and 29% were ApoE ε4 noncarriers. Fifty-seven percent of patients were female, 91% were White, 6% were Asian, 4% were Hispanic or Latino, and 2% were Black or African American.

The primary efficacy endpoint was change in the integrated Alzheimer's Disease Rating Scale (iADRS) score from baseline to 76 weeks. The iADRS is a combination of two scores: the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog_{13}) 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. Other efficacy endpoints included Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB), ADAS-Cog_{13}, and ADCS-iADL.

There were two primary analysis populations based on tau PET imaging with flortaucipir: 1) low/medium tau level population (defined by visual assessment and SUVR of ≥1.10 and ≤1.46), and 2) combined population of low/medium plus high tau (defined by visual assessment and SUVR >1.46) population.

Patients treated with Kisunla demonstrated a statistically significant reduction in clinical decline on iADRS compared to placebo at Week 76 in the combined population (2.92, $p<0.0001$) and the low/medium tau population (3.25, $p<0.0001$).

Patients treated with Kisunla demonstrated a statistically significant reduction in clinical decline on CDR-SB compared to placebo at Week 76 in the combined population (-0.70, $p<0.0001$) (see Table 2). There were also statistically significant differences ($p<0.001$) between treatment groups as measured by ADAS-Cog_{13} and ADCS-iADL at Week 76 (see Table 2).

Dosing was continued or stopped in response to observed effects on amyloid imaging. The percentages of patients eligible for switch to placebo based on amyloid PET levels at Week 24, Week 52, and Week 76 timepoints were 17%, 47%, and 69%, respectively. Amyloid PET values may increase after treatment with donanemab is stopped. There is no data beyond the 76-week duration of Study 1 to guide whether additional dosing with Kisunla may be needed for longer-term clinical benefit.

Table 2. Efficacy Analysis Results in Combined Population at Week 76 in Study 1

Clinical Endpoints	Kisunla (N=860)	Placebo (N=876)
CDR-SB[a]		
Mean baseline	3.92	3.89
Adjusted mean change from baseline	1.72	2.42
Difference from placebo (%)[c]	-0.70 (29%) P<0.0001	--
ADAS-Cog$_{13}$[b]		
Mean baseline	28.53	29.16
Adjusted mean change from baseline	5.46	6.79
Difference from placebo (%)[c]	-1.33 (20%) P=0.0006	--
ADCS-iADL[c]		
Mean baseline	47.96	47.98
Adjusted mean change from baseline	-4.42	-6.13
Difference from placebo (%)[c]	1.70 (28%) P=0.0001	--

ADAS-Cog$_{13}$: Alzheimer's Disease Assessment Scale – 13-item Cognitive Subscale; ADCS-iADL: Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living subscale; CDR-SB: Clinical Dementia Rating Scale – Sum of Boxes.

[a] Assessed using mixed model for repeated measures analysis.

[b] Assessed using natural cubic spline with 2 degrees of freedom analysis.

[c] Percent slowing of decline relative to placebo: difference of adjusted mean change from baseline between treatment groups divided by adjusted mean change from baseline of placebo group at Week 76.

Study 2

Study 2 (NCT0337403) was a randomized, double-blind study investigating the effect of different Kisunla dosing regimens on ARIA-E and change from baseline in amyloid in adults with Alzheimer's disease (patients with confirmed amyloid pathology and mild cognitive impairment or mild dementia stage of disease). Inclusion and exclusion criteria were the same as Study 1 except that tau PET was not an inclusion criterion. Patients were randomized to receive Dosing Regimen 1 (N=207), or one of three alternative regimens, including Dosing Regimen 2 (N=212) in a 1:1:1:1 ratio. The treatment period was up to 72 weeks, and treatment stopping criteria based on amyloid PET were the same as Study 1.

Of the 212 patients receiving Dosing Regimen 2, the mean age was 74 years. Fifty-nine percent were female, 91% were White, 6.6% were Black or African American, 5.2% were Hispanic or Latino, and 1.4% were Asian. Overall, 65% of these patients were ApoE ε4 carriers, with 55% heterozygotes and 10% homozygotes, and 36% were noncarriers.

The primary endpoint of the study was the proportion of patients with any occurrence of ARIA-E. The results showed that patients receiving Dosing Regimen 2 had less incidence of ARIA-E by Week 52 compared with patients receiving Dosing Regimen 1 (see Table 3).

ARIA-E occurred at a higher incidence in ApoE ε4 homozygotes, compared to heterozygotes, with the lowest incidence in noncarriers. The small number of events and limited exposure in the ApoE ε4 subgroups limit definitive conclusions about the risk of ARIA-E.

Table 3. Cumulative Incidence of ARIA-E and ARIA-H in 52 Weeks, Overall and by ApoE e4 Genotype, in Study 2

	Dosing Regimen 1 N=207	**Dosing Regimen 2 N=212**
ARIA-E Overall		
n (incidence, %)	50 (24.9)	33 (16.2)
RD (95% CI)	-	8.7 (0.8, 16.5)
ARIA-H Overall		
n (incidence, %)	56 (28.1)	51 (25.2)
RD (95% CI)	-	2.9 (-5.8, 11.6)
Homozygotes, N	21	21
ARIA-E		
n (incidence[1], %)	12 (57.1)	5 (24.4)
RD (95% CI)	-	32.7 (4.4, 60.9)
ARIA-H		
n (incidence[1], %)	10 (47.6)	6 (28.6)
RD (95% CI)	-	19.0 (-9.8, 47.8)
Heterozygotes, N	112	115
ARIA-E		
n (incidence[1], %)	27 (25.0)	18 (16.4)
RD (95% CI)	-	8.6 (-2.2, 19.3)
ARIA-H		
n (incidence[1], %)	34 (31.8)	33 (30.8)
RD (95% CI)	-	1.0 (-11.5, 13.5)
ApoE noncarriers, N	72	75
ARIA-E		
n (incidence[1], %)	11 (15.6)	10 (13.8)
RD (95% CI)	-	1.8 (-9.8, 13.5)
ARIA-H		
n (incidence[1], %)	12 (17.2)	12 (16.4)
RD (95% CI)	-	0.8 (-11.5, 13.1)

CI: confidence interval; RD: risk difference; ApoE e4: apolipoprotein E ε4; ARIA-E: amyloid related imaging abnormalities with edema; ARIA-H: amyloid related imaging abnormalities with hemosiderin deposition.
[1] Kaplan-Meier estimates of cumulative incidence.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J0175

*Current Procedural Terminology (CPT®) ©2025 American Medical Association: Chicago, IL.

References

U.S. Food and Drug Administration Label:

1. U.S. Food and Drug Administration, Drugs@FDA. Highlights of Prescribing Information: Kisunla (donanemab-azbt). (7/2025). Available at accessdata.fda.gov (accessed July 30, 2025).

Other:

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Centers for Medicare &Medicaid Services

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare & Medicaid Services does have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at cms.hhs.gov.

Policy History/Revision

Date	Description of Change
5/7/2026	New medical document. Donanemab-azbt (Kisunla) may be considered medically necessary for the treatment of Alzheimer's Disease when ALL the following criteria are met: Individual is aged 50 years or older; AND Individual has mild cognitive impairment due to AD or mild AD dementia; AND Individual has positive amyloid load as indicated by one of the following: Positron emission tomography assessment of imaging agent uptake into brain; or Cerebrospinal fluid assessment of amyloid β (Aβ1-42); AND Individual has a baseline brain magnetic resonance imaging (MRI) prior to initiating treatment; AND Individual must have one of the following scores at baseline on any of the following assessment tools: Clinical Dementia Rating-Global Score (CDR-GS) of 0.5 or 1; or Mini-Mental Status Examination score of 22-28. Donanemab-azbt (Kisunla) is considered experimental, investigational and/or unproven for all other non-Food and Drug Administration approved indications.