09-J4000-94

Original Effective Date: 09/15/24

Reviewed: 02/12/25

Revised: 03/15/25

Subject: Donanemab-azbt (Kisunla) intravenous infusion

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DESCRIPTION:

Alzheimer's disease (AD) is a gradual, progressive dementia that impacts memory and cognition typically in patients 65 years of age and older. Its prevalence is estimated to be 1-2% of patients less than or equal to 65 years and increases with age to approximately 30-50% of patients at 85 years. Risk factors for the development of AD include diabetes, hypertension, dyslipidemia, metabolic syndrome, obesity, smoking, cerebrovascular injury, female sex, family history of AD, and the presence of the epsilon-4 allele of the *APOE* gene. Neurological findings consistent with AD include the presence of neurofibrillary tangles of tau protein and beta-amyloid plaques. AD is a debilitating disease as it eventually impairs the patient's ability to conduct daily activities and causes additional psychological symptoms including, but not limited to, anxiety, depression, confusion, agitation, delusions, and hallucinations. Following diagnosis at 60-69 years of age, the estimated median survival is approximately 6.7 years.

Management of AD is guided by dementia severity. Standard therapeutic options include acetylcholinesterase inhibitors (i.e., donepezil, rivastigmine, galantamine) for all stages of dementia and memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, for moderate-to-severe AD. In June 2021, aducanumab-avwa (Aduhelm), a human, immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against amyloid beta, was FDA approved via the accelerated pathway based on a reduction in amyloid beta plaques in mild AD; however, the agent did not demonstrate any clinical improvement in patients and had limited therapeutic utility outside of clinical trials. Therefore, the manufacturer of aducanumab-avwa (Aduhelm) decided to withdrawal the product from the US market in early 2024.

On January 6, 2023, the FDA approved lecanemab-irmb (Leqembi), another human, immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against amyloid beta for the treatment of AD patients with mild cognitive impairment (MCI) or mild dementia stage of the disease, via the accelerated pathway and subsequently provided traditional approval on July 6, 2023. On July 2, 2024, the FDA

approved donanemab-azbt (Kisunla), an amyloid beta-directed antibody, for the treatment of AD patients with mild cognitive impairment (MCI) or mild dementia stage of the disease.

The efficacy and safety of donanemab-azbt (Kisunla) was evaluated in a double-blind, placebo-controlled, parallel-group study in patients with AD confirmed by the presence of amyloid pathology and mild cognitive impairment or mild dementia stage of disease (i.e., Stage 3 and Stage 4). Enrolled patients had a Mini-Mental State Examination (MMSE) score of ≥ 20 and ≤ 28, a progressive change in memory function for at least 6 months and were included based on visual assessment of tau PET imaging with flortaucipir and standardized uptake value ratio (SUVR). Concomitant AD therapies was allowed (e.g., cholinesterase inhibitors, memantine). A total of 1,736 patients were randomized 1:1 to receive either 700 mg of donanemab-azbt (Kisunla) every 4 weeks for the first 3 doses, and then 1,400 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 weeks 24, 52, and 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 (range: 59 – 86 years). Of the total number of patients randomized, 68% had low/medium tau level and 32% had high tau level; 71% were ApoE ε4 carriers and 29% were ApoE ε4 noncarriers. Fifty-seven percent of patients were female, 91% were Caucasian, 6% were Asian, 4% were Hispanic or Latino, and 2% were 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-Cog13) 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-Cog13, 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 donanemab-azbt (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). Table 1 provides the summary results in the combined population at Week 76.

Table 1: Efficacy Analysis Results in the Combined Population at Week 76[a]

Clinical Endpoints	**Donanemab-azbt (Kisunla) (N = 860)**	**Placebo (N = 876)**
CDR-SB[b]		
Mean baseline	3.92	3.89
Adjusted mean change from baseline	1.72	2.42
Difference from placebo (%)[d]	-0.70 (29%) p<0.0001	---
ADAS-Cog13[c]		
Mean baseline	28.53	29.16
Adjusted mean change from baseline	5.46	6.79
Difference from placebo (%)[d]	-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 (%)[d]	1.70 (28%) P=0.0001	---

[a]Abbreviations: ADAS-Cog13 = 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; NCS2 = natural cubic spline with 2 degrees of freedom; MMRM = mixed model for repeated measures.
[b]Assessed using MMRM analysis.
[c]Assessed using NCS2 analysis.
[d]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.

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 weeks 24, 52, and 76 timepoints were 17%, 47%, and 69%, respectively. Amyloid PET values may increase after treatment with donanemab is stopped; however, there is no data beyond the 76-week duration to guide whether additional dosing with donanemab-azbt (Kisunla) may be needed for longer-term clinical benefit.

The most common adverse reactions (at least 10% and higher incidence compared to placebo) include ARIA-E, ARIA-H microhemorrhage, ARIA-H superficial siderosis, and headache.

POSITION STATEMENT:

Administration of donanemab-azbt (Kisunla) **meets the definition of medical necessity** when ALL of the following are met:

1. Member is 50 to 90 years of age
2. Diagnosis of mild cognitive impairment (MCI) due to Alzheimer's Disease (AD) or mild AD dementia with "mild disease" documented by all of the following within the last 6 months ("i", "ii", and "iii"): - Documentation must be provided
    i. Clinical Dementia Rating (CDR)-Global Score of 0.5-1.0
    ii. CDR Memory Box Score of at least 0.5
    iii. Mini-Mental Status Exam (MMSE) score between 20-30, inclusive
3. Member has been previously receiving lecanemab-irmb (Leqembi) therapy for AD and one of the following ("i" or "ii"): – Documentation must be provided
    i. Disease severity has progressed from baseline within the last 6 months but has not progressed to moderate or severe AD based on one of the following objective measure tools ("a", "b", "c" or "d"):
        a. Mini-Mental Status Exam (MMSE)
        b. Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog-13)
        c. Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory-Mild Cognitive Impairment version (ADCS-ADL-MCI)
        d. Clinical Dementia Rating-Sum of Boxes [CDR-SB]

ii. Documentation of intolerance to lecanemab-irmb (Leqembi) therapy and no progression to moderate or severe AD based on one of the following objective measure tools ("a", "b", "c", or "d"):

   a. Mini-Mental Status Exam (MMSE)

   b. Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog-13)

   c. Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory-Mild Cognitive Impairment version (ADCS-ADL-MCI)

   d. Clinical Dementia Rating-Sum of Boxes [CDR-SB]

4. Positron Emission Tomography (PET) scan or CSF assessment of Aß (1-42) within the last 1 year is positive for amyloid beta plaque – Documentation must be provided
5. Baseline brain magnetic resonance imaging (MRI) obtained within 1 year prior to initiation of treatment with none of the following risk factors for intracerebral hemorrhage present – Documentation must be provided
   i. More than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter)
   ii. A single macrohemorrhage >10 mm at the greatest diameter
   iii. An area of superficial siderosis
   iv. Evidence of vasogenic edema
   v. Evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions
   vi. Evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease
   vii. Space occupying lesions
   viii. Brain tumors (except those diagnosed as meningiomas or arachnoid cysts and <1 cm at their greatest diameter);
6. If concomitantly taking an antithrombotic medication (e.g., aspirin, other antiplatelets, or anticoagulants) the dose has been stable for at least 4 weeks.
7. Member has been informed that those who are apolipoprotein E ε4 (ApoE ε4) homozygotes have a higher incidence of developing ARIA.
8. **NOT** prescribed in combination with lecanemab-irmb (Leqembi)
9. The medication is prescribed by a neurologist, neuropsychiatrist, or geriatric specialist with experience in treating dementia
10. The dosage does not exceed 700 mg IV every 4 weeks for 3 doses, then 1,400 mg IV every 4 weeks

Approval duration: 6 months

Donanemab-azbt (Kisunla) is considered **experimental or investigational** for any other indications due to insufficient evidence in the peer-reviewed medical literature to support safety, efficacy, and net health outcome.

Continuation of donanemab-azbt (Kisunla) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Authorization/reauthorization for the requested agent has been previously approved by Florida Blue or another health plan in the past 2 years (if another health plan, documentation of a health plan-paid claim during the 90 days before the authorization request must be submitted), OR the member currently meets all indication-specific initiation criteria.
2. MRIs have been obtained prior to the 2nd, 3rd, 4th, AND 7th infusion for monitoring of Amyloid Related Imaging Abnormalities-edema (ARIA-E) and Amyloid Related Imaging Abnormalities-hemosiderin (ARIA-H) microhemorrhages – Documentation must be provided
3. Member has not experienced any adverse effects such as amyloid related imaging abnormalities-edema (ARIA-E) and -hemosiderin deposition (ARIA-H), intracerebral hemorrhage, or severe hypersensitivity reactions necessitating discontinuation of therapy.
4. Member has not progressed to moderate or severe AD and responded to therapy compared to their pre-treatment baseline as evidenced by improvement, stability, or slowing in cognitive and/or functional impairment (e.g., ADAS-Cog 13; ADCS-ADL-MCI; MMSE; CDR-SB) – Documentation must be provided using the same disease severity tool used at baseline
5. Amyloid plaque levels have **NOT** reached ONE of the following criteria for discontinuation of donanemab-azbt (Kisunla) therapy ("a" or "b"): - Documentation must be provided
    a. Level is less than 11 Centiloids on a single PET scan
    b. Level is 11 to less than 25 Centiloids on two consecutive PET scans
6. **NOT** prescribed in combination with lecanemab-irmb (Leqembi)
7. The medication is prescribed by**,** or in consultation with, a neurologist, neuropsychiatrist, or geriatric specialist with experience in treating dementia
8. The dosage does not exceed 700 mg IV every 4 weeks for 3 doses, then 1,400 mg IV every 4 weeks

Approval duration: 6 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Donanemab-azbt (Kisunla) is indicated for the treatment of Alzheimer's disease. Treatment with 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.
- The recommended dosage is 700 mg via IV infusion every 4 weeks for 3 doses, then 1,400 mg IV infusion every 4 weeks.
- Dilution to a final concentration of 4 mg/mL to 10 mg/mL with 0.9% sodium chloride Injection, is required prior to administration.

- The infusion should be administered over approximately 30 minutes.
- Obtain a recent brain MRI prior to initiating treatment to evaluate for pre-existing Amyloid Related Imaging Abnormalities (ARIA) and prior to the 2nd, 3rd, 4th, and 7th infusions. If radiographically observed ARIA occurs, treatment recommendations are based on type, severity, and presence of symptoms.
- Consider stopping dosing with donanemab-azbt (Kisunla) based on reduction of amyloid plaques to minimal levels on amyloid PET imaging.

Dose Adjustments

Table 1: Dosing Recommendations for Patients with ARIA-E

Clinical Symptom Severity[1]	ARIA-E Severity on MRI		
	Mild	**Moderate**	**Severe**
Asymptomatic	May continue dosing	Suspend dosing[2]	Suspend dosing[2]
Mild	May continue dosing based on clinical judgment	Suspend dosing[2]	
Moderate or Severe	Suspend dosing[2]		

1 Mild: discomfort noticed, but no disruption of normal daily activity.
Moderate: discomfort sufficient to reduce or affect normal daily activity.
Severe: incapacitating, with inability to work or to perform normal daily activity.

2. Suspend until MRI demonstrates radiographic resolution and symptoms, if present, resolve; consider a follow-up MRI to assess for resolution 2 to 4 months after initial identification. Resumption of dosing should be guided by clinical judgment.

Table 2: Dosing Recommendations for Patients with ARIA-H

Clinical Symptom Severity'	ARIA-H Severity on MRI		
	Mild	**Moderate**	**Severe**
Asymptomatic	May continue dosing	Suspend dosing[1]	Suspend dosing[2]
Symptomatic	Suspend dosing[1]	Suspend dosing[1]	

1. Suspend until MRI demonstrates radiographic stabilization and symptoms, if present, resolve; resumption of dosing should be guided by clinical judgment; consider a follow-up MRI to assess for stabilization 2 to 4 months after initial identification.
2. Suspend until MRI demonstrates radiographic stabilization and symptoms, if present, resolve; use clinical judgment in considering whether to continue treatment or permanently discontinue donanemab-azbt (Kisunla).

- In patients who develop intracerebral hemorrhage greater than 1 cm in diameter during treatment with donanemab-azbt (Kisunla), suspend dosing until MRI demonstrates radiographic stabilization and symptoms, if present, resolve. Resumption of dosing should be guided by clinical judgment.

Drug Availability

- 350 mg/20 mL (17.5 mg/mL) in a single-dose vial

PRECAUTIONS:

Boxed Warning

- **Amyloid Related Imaging Abnormalities**: Monoclonal antibodies directed against aggregated forms of beta amyloid, including donanemab-azbt (Kisunla), can cause amyloid related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E) and ARIA with hemosiderin deposition (ARIA-H). ARIA is usually asymptomatic, although rarely serious and life-threatening events can occur. Serious intracerebral hemorrhage greater than 1 cm have occurred in patients treated with this class of medications. ARIA-E can cause focal neurologic deficits that can mimic ischemic stroke.
- **ApoE ε4 Homozygotes**: Patients treated with this class of medications, including donanemab-azbt (Kisunla), who are ApoE ε4 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 initiation of treatment to inform the risk of developing ARIA. Prior to testing, prescribers should discuss with patients the risk of ARIA across genotypes and the implications of genetic testing results.
- Consider the benefit for the treatment of Alzheimer's disease and risk of ARIA when deciding to treat with donanemab-azbt (Kisunla).

Contraindications

- Donanemab-azbt (Kisunla) is contraindicated in patients with known serious hypersensitivity to donanemab-azbt or to any of the excipients.

Precautions/Warnings

- **Amyloid Related Imaging Abnormalities (ARIA):** Enhanced clinical vigilance for ARIA is recommended during the first 24 weeks of treatment with donanemab-azbt (Kisunla). Risk of ARIA, including symptomatic ARIA, was increased in apolipoprotein E ε4 homozygotes compared to heterozygotes and noncarriers. The risk of ARIA-E and ARIA-H is increased in with donanemab-treated patients with pretreatment microhemorrhages and/or superficial siderosis. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including MRI scanning if indicated.
- **Infusion-Related Reactions:** The infusion rate may be reduced, or the infusion may be discontinued, and appropriate therapy initiated as clinically indicated. Consider pre-treatment with antihistamines, acetaminophen, or corticosteroids prior to subsequent dosing.
- **Use of Antithrombotic or Thrombotic Medications:** Caution should be exercised when considering donanemab-azbt (Kisunla) in patients with factors that indicate an increased risk for intracerebral hemorrhage and in particular for patients who need to be on anticoagulant therapy or patients with findings on MRI that are suggestive of cerebral amyloid angiopathy.
- **Patients with Risk Factors for Intracerebral Hemorrhage:** Caution should be exercised when

considering donanemab-azbt (Kisunla) in patients with intracerebral hemorrhage risk factors.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J0175	Injection, donanemab-azbt, 2 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

G30.0 – G30.9	Alzheimer's disease

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

Section 1: Standard CDR

Please enter scores below.	IMPAIRMENT				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
1. MEMORY	No memory loss, or slight inconsistent forgetfulness.	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness.	Moderate memory loss, more marked for recent events; defect interferes with everyday activities.	Severe memory loss; only highly learned material retained; new material rapidly lost.	Severe memory loss; only fragments remain.
2. ORIENTATION	Fully oriented.	Fully oriented except for slight	Moderate difficulty with time	Severe difficulty with time	Oriented to person only.

		difficulty with time relationships.	relationships; oriented for place at examination; may have geographic disorientation elsewhere.	relationships; usually disoriented to time, often to place.	
3. JUDGMENT AND PROBLEM SOLVING	Solves everyday problems. Handles business and financial affairs well; judgment good in relation to past performance.	Slight impairment in these activities.	Moderate difficulty in handling problems, similarities and differences; social judgment usually maintained.	Severely impaired in handling problems, similarities and differences; social judgment usually impaired.	Unable to make judgments or solve problems.
4. COMMUNITY AFFAIRS	Independent function at usual level in job. shopping, volunteer and social groups.	Life at home, hobbies and intellectual interests slightly impaired.	Unable to function independently at these activities, although may still be engaged in some; appears normal to casual inspection.	No pretense of independent function outside the home; appears well enough to be taken to functions outside the family home.	No pretense of independent function outside the home; appears too ill to be taken to functions outside the family home.
5. HOME & HOBBIES	Life at home. hobbies and intellectual interests well maintained.	Life at home, hobbies, and intellectual interests slightly impaired.	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned.	Only simple chores preserved; very restricted interests: poorly maintained.	No significant function in the home.
6. PERSONAL CARE	Fully capable of self-care.		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects.	Requires much help with personal care; frequent incontinence.

Sum of Boxes Staging Category

CDR Sum of Boxes Range	Staging Category
0	Normal
0.5-4.0	Questionable cognitive impairment
0.5-2.5	Questionable impairment
3.0-4.0	Very mild dementia
4.5-9.0	Mild dementia
9.5-15.5	Moderate dementia

16.0-18.0	Severe dementia

RELATED GUIDELINES:

Lecanemab-irmb (Leqembi) intravenous infusion, 09-J4000-41

OTHER:

None

REFERENCES:

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3. Kisunla (donanemab-azbt) [package insert]. Eli Lilly and Company, Indianapolis (IN) July 2024.
4. Micromedex Healthcare Series [Internet Database]. Greenwood Village, CO: Thomson Healthcare. Updated periodically. Accessed 11/25/24.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 02/12/25.

GUIDELINE UPDATE INFORMATION:

09/15/24	New Medical Coverage Guideline – Donanemab-azbt (Kisunla) for the treatment of Alzheimer's disease patients with mild cognitive impairment or mild dementia stage of the disease.
10/01/24	Revision: Added HCPCS code J0175 and deleted codes C9399 and J3590.
01/15/25	Review and revision to guidelines consisting of revising the position statement to require lecanemab (Leqembi) therapy prior to donanemab (Kisunla) therapy for AD patients with mild cognitive impairment or mild dementia stage of the disease and updating references.
03/15/25	Review and revision to the guideline consisting of revising the Position Statement to extend the range for the MMSE assessment from 22-30 to 20-30 for "mild cognitive impairment" and the baseline assessment for amyloid beta plaque from 6 months to 1 year.