Donanemab-azbt (KISUNLA)
National Drug Monograph
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VA Pharmacy Benefits Management Services and VA National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Donanemab is an immunoglobulin G1 monoclonal antibody directed against insoluble, modified, N-terminal truncated form of s-amyloid present only in brain amyloid plaques.

Indication(s) Under Review in This Document

Donanemab is indicated for the treatment of mild cognitive impairment (MCI) or mild dementia secondary to Alzheimer's disease, the population in which treatment was initiated in the clinical trials.

Dosage Form(s) Under Review

- Injection: 350mg/20ml single dose vial; 700mg is to be given as an intravenous (IV) infusion over 30 minutes every 4 weeks for the first three doses, followed by 1400mg every 4 weeks.

Clinical Evidence Summary[5-7]

Efficacy Considerations

- The efficacy of donanemab, supporting its FDA approval, was evaluated from industry-sponsored studies, including a phase 2b, early Alzheimer disease trial (TRAILBLAZER-ALZ, NCT03367403, Mintun et al) and an 18-month, multicenter, double-blind, phase 3 trial (TRAILBLAZER-ALZ-2, AACI, NCT04437511, Sims et al).
- TRAILBLAZER-ALZ (N=257) included patients 60 to 85 years of age who had early symptomatic Alzheimer's disease (MCI) or mild dementia due to Alzheimer's disease and had a Mini–Mental State Examination (MMSE) score of 20 to 28. Patients were required to have PET scans with evidence of pathologic tau deposits. Patients received donanemab (N=131; 700 mg x 3 doses and 1400 mg thereafter) or placebo (N=126), administered intravenously every 4 weeks for up to 72 weeks. In participants who were treated with donanemab, if the amyloid plaque level as assessed by florbetapir PET (performed at 24 and 52 weeks) was 11 to <25 Centiloids, the dose was lowered to 700 mg. If the amyloid plaque level was less than 11 Centiloids on any one scan or was 11 to <25 Centiloids on two consecutive scans, donanemab was switched to placebo.

- The primary outcome was the change from baseline to 76 weeks in the score on the Integrated Alzheimer's Disease Rating Scale (iADRS; scores range from 0 to 144, with lower scores indicating a greater cognitive deficit and greater impairment of the ability to perform instrumental activities of daily living).
- The iADRS is a combination of the 13-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog13; scores range from 0 to 85, with higher scores indicating a greater deficit) and the Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living Inventory (ADCS-iADL; scores range from 0 to 59, with lower scores indicating greater impairment). An iADRS score of 5 points for MCI due to AD and 9 points for AD with mild dementia are considered thresholds for minimal clinically important difference (MCID).
- The change from baseline in the iADRS score at 76 weeks was -6.86 in the donanemab group and -10.06 in the placebo group (difference, 3.20; 95% confidence interval [CI], 0.12 to 6.27;P = 0.04). The results for most secondary outcomes including CDR-SB, ADAS-Cog13, ADCS-iADL, MMSE showed no substantial difference.
- TRAILBLAZER-ALZ-2 included participants aged 60 to 85 years with MCI or Alzheimer disease with mild dementia, had screening MMSE scores of 20 to 28, amyloid pathology ($\geq$37 Centiloids), and presence of tau pathology. Tau PET scans were categorized as low/medium or high tau. Key exclusion criteria included presence of amyloid-related imaging abnormalities of edema/effusion, more than 4 cerebral microhemorrhages, more than 1 area of superficial siderosis, any intracerebral hemorrhage greater than 1 cm or severe white matter disease on MRI. Subjects received either donanemab (N=860, 700 mg for the first 3 doses and 1400 mg thereafter) or placebo (N=876), administered intravenously every 4 weeks for up to 72 weeks. Like TRAILBLAZER-ALZ, if amyloid plaque level (assessed at 24 weeks and 52 weeks) was less than 11 Centiloids on any single PET scan or 11 to < 25 Centiloids on 2 consecutive PET scans, donanemab was switched to placebo. The Centiloid scale is a method designed to standardize PET data. It is a 100-point scale termed "Centiloid," in which an average value of zero means there is "high certainty" that the subject is amyloid negative and an average of 100 is correlated with the "typical" AD patients (Klunk et al., 2015). A Centiloid value > 30 is consider elevated. Key inclusion and exclusion criteria and baseline characteristics are included in Table 1 and 2 respectively.
- The primary outcome was change in the iADRS score from baseline to 76 weeks in either the low/medium tau population or combined (low/medium and high tau) population. In the low/medium tau population, least-squares mean (LSM) change from baseline in the iADRS score at 76 weeks was -6.02 (95% CI, -7.01 to -5.03) in the donanemab group and -9.27 (95% CI, -10.23 to -8.31) in the placebo group (difference, 3.25 [95% CI, 1.88-4.62]; P < .001). In the combined population, LSM change from baseline in the iADRS score at 76 weeks was -10.19 (95%CI, -11.22 to-9.16) in the donanemab group and -13.11 (95%CI, -14.10 to -12.13) in the placebo group (difference, 2.92 [95% CI, 1.51-4.33]; P < .001). See Table 3 for more information.
- Prespecified secondary outcomes included changes from baseline to 76 weeks by sum of boxes of the Clinical Dementia Rating Scale (CDR-SB), the ADAS-Cog13, the ADCS-iADL, MMSE, and amyloid plaque reduction in the low/medium tau or combined population. The percentage of participants reaching amyloid clearance (<24.1 Centiloids measured by amyloid PET) at 24

weeks and 76 weeks, in the combined group was 29.7% and 76.4% respectively. See Table 4 for more information.

- The CDR-SB is a measure of cognition and function in AD on a scale of 0 to 18 that can change in increments of 0.5 or higher. A higher score indicates greater disease severity. The measure includes three domains relating to cognition (memory, orientation, judgment/problem-solving) and three domains related to function (community affairs, home/hobbies, personal care). The CDR-SB MCID is 1 point for MCI and 2 points for mild AD. The MMSE is a cognitive performance tool with scores ranging from 0 to 30. Higher scores indicate less cognitive impairment. The MMSE MCID is 1 point for MCI and 2 points for mile AD.

Table 1. Key Inclusion and Exclusion Criteria for TRAILBLAZER-ALZ-2[7]

Inclusion

- 60 to 85 years of age
- Gradual and progressive change in memory function reported by the participant or informant for ≥ 6 months
- An MMSE score of 20 to 28
- Amyloid pathology (≥37 Centiloids)
- Have adequate literacy, vision, and hearing for neuropsychological testing in the opinion of the investigator at the time of screening.
- Stable concomitant symptomatic AD medications and other medications that may impact cognition for at least approximately 30 days prior to randomization

Exclusion

- Significant neurological disease affecting the central nervous system other than AD, that may affect cognition or ability to complete the study, including but not limited to, other dementias, serious infection of the brain, Parkinson's disease, multiple concussions, or epilepsy or recurrent seizures (except febrile childhood seizures).
- Current serious or unstable illnesses including cardiovascular, hepatic, renal, gastroenterological, respiratory, endocrinologic, neurologic (other than AD), psychiatric, immunologic, or hematologic disease
- History of cancer within the last 5 years, except for non-metastatic basal and/or squamous cell carcinoma of the skin, in situ cervical cancer, nonprogressive prostate cancer, or other cancers with low risk of recurrence or spread.
- Participants with any current primary psychiatric diagnosis other than AD if, in the judgment of the investigator, the psychiatric disorder or symptom is likely to confound interpretation of drug effect, affect cognitive assessment, or affect the participant's ability to complete the study. Participants with history of schizophrenia or other chronic psychosis are excluded.
- Actively suicidal
- History of alcohol or drug use disorder (except tobacco use disorder) within 2 years before the screening visit.
- History of clinically significant multiple or severe drug allergies, significant atopy, or severe posttreatment hypersensitivity reactions (including but not limited to erythema multiforme

major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, and/or exfoliative dermatitis).

- Have any clinically important abnormality in physical or neurological examination, vital signs, ECG, or clinical laboratory test results that could be detrimental to the participant, could compromise the study, or show evidence of other etiologies for dementia.
- Contraindications for MRI
- An MRI which shows evidence of significant abnormality or demonstrating presence of ARIA-E, >4 cerebral microhemorrhages, more than 1 area of superficial siderosis, any macro hemorrhage or severe white matter disease
- Contraindication to PET
- Present or planned exposure to ionizing radiation that, in combination with the planned administration of study PET ligands, would result in a cumulative exposure that exceeds local recommended exposure limits.
- Alanine aminotransaminase (ALT) >/= 2.5 X the upper limit of normal (ULN) of the performing laboratory, aspartate aminotransferase (AST) >/= 2.5 x ULN, total bilirubin level (TBL) >/= 1.5 x ULN, or alkaline phosphatase (ALP) >/= 2 x ULN
- Have had prior treatment with a passive anti-amyloid immunotherapy <5 half-lives prior to randomization
- Have received active immunization against Aβ in any other study

Table 2. Baseline Characteristics of TRAILBLAZER-ALZ-2 Participants [6]

Characteristic	**Donanemab N=860**	**Placebo N=876**
Age, years, mean	73	73
% Female	57.3	57.4
Race/ethnicity (US only), n (%)		
White	591/619 (95.5)	612/632 (96.8)
Black	18/619 (2.9)	16/632 (2.5)
Asian	8/619 (1.3)	3/632 (0.5)
Hispanic	35 (5.7)	36 (5.7)
Non-Hispanic	583 (94.3)	594 (94.3)
Concomitant AD medication (%)	60.6	61.4
ApoE e4 carrier, n (%)	598 (69.8)	621 (71.2)
ApoE e4 heterozygote	433 (50.5)	450 (51.6)
ApoE e4 homozygote	143 (16.7)	146 (16.7)
Global CDR score, n (%)		
0.5	514 (60.8)	532 (61.2)
1	304 (36.0)	308 (35.4)
2	25 (3.0)	25 (2.9)
MMSE score, (SD)	22.4 (3.8)	22.2 (3.9)
Stage of disease, n (%)		
MCI due to AD	146 (17)	137 (15.7)

Mild dementia due to AD	713 (82.9)	738 (84.3)

AD: Alzheimer disease; MMSE: Mini mental state exam; MCI: mild cognitive impairment

Table 3. Primary Endpoint, TRAILBLAZER-ALZ-2, iADRS change from baseline to 76 weeks in low/medium tau and combined populations[6]

	Donanemab	**Placebo**
Low/medium tau	N=533	N=560
Baseline, mean (SD)	105.92 (13.72)	105.95 (13.42)
LSM change (95% CI)	-6.02 (-7.01 to -5.03)	-9.27 (-10.23 to -8.31)
LSM difference vs placebo (95% CI)	**3.25 (1.88 to 4.62)**	-
p-value vs placebo	<0.001	-
Combined group	N=775	N=824
Baseline, mean (SD)	104.55 (13.90)	103.82 (13.88)
LSM change (95% CI)	-10.19 (-11.22 to -9.16)	-13.11 (-14.10 to -12.13)
LSM difference vs placebo (95% CI)	**2.92 (1.51 to 4.33)**	-
P value vs placebo	<0.001	-
Minimal clinically important difference	**5 points, MCI; 9 points, mild AD**	-

CI: confidence interval; iADRS: Integrated Alzheimer's Disease Rating Scale; LSM: least squares mean; MCI: mild cognitive impairment; SD: standard deviation.

Table 4. Secondary Endpoints, TRAILBLAZER-ALZ-2, change from baseline to 76 weeks in low/medium tau and combined populations[6]

Endpoint	**Donanemab**	**Placebo**
Amyloid plaque level, Centiloids Low/medium tau	N=588	N=594
Mean Baseline (SD)	102.4 (34.7)	100.9 (35.1)
LSM change (95% CI)	-88.0 (-90.20 to -85.87)	0.2 (-1.91 to 2.26)
Combined group	N=860	N=876
Mean Baseline (SD)	103.5 (34.5)	101.6 (34.5)

LSM change (95% CI)	-87.0 (-88.90 to -85.17)	-0.67 (-2.45 to 1.11)
ADAS-cog13 score Low/medium tau	N=550	N=570
Mean Baseline (SD)	27.41 (8.44)	27.60 (8.21)
LSM change (95% CI)	3.17 (2.64 to 3.69)	4.69 (4.18 to 5.20)
LSM difference vs placebo (95%CI)	**1.52 (-2.25 to -0.79)**	
p-value vs. placebo	<0.001	
Combined group	N=797	N=841
Mean Baseline (SD)	28.53 (8.78)	29.16 (8.85)
LSM change (95% CI)	5.46 (4.91 to 6.01)	6.79 (6.26 to 7.32)
LSM difference vs placebo (95%CI)	**-1.33 (-2.09 to -0.57)**	
p-value vs. placebo	<0.001	
Minimal clinically important difference	**2 points, MCI; ≥3 points for mild AD**	
CDR-SB ***Low/medium tau***	N=546	N=569
Mean Baseline (SD)	3.72 (2.09)	3.64 (1.99)
LSM change (95% CI)	1.16 (0.97 to 1.35)	1.84 (1.65 to 2.02)
LSM difference vs placebo (95%CI)	**-0.68 (-0.94 to -0.42)**	
p-value vs. placebo	<0.001	
Combined group	N=794	N=838
Mean Baseline (SD)	3.92 (2.06)	3.89 (2.03)
LSM change (95% CI)	1.66 (1.48 to 1.83)	2.33 (2.16 to 2.50)
LSM difference vs placebo (95%CI)	**-0.67 (-0.92 to -0.43)**	
p-value vs. placebo	<0.001	
Minimal clinically important difference	**1 point, MCI; 2 points, mild AD**	

ADCS-iADL Low/medium tau	N=535	N=562
Mean Baseline (SD)	48.20 (7.88)	48.56 (7.70)
LSM change (95% CI)	-2.76 (-3.42 to -2.10)	-4.59 (-5.23 to -3.95)
LSM difference vs placebo (95%CI)	**1.83 (0.91 to 2.75)**	
p-value vs. placebo	<0.001	
Combined group	N=780	N=826
Mean Baseline (SD)	47.96 (7.85)	47.98 (7.70)
LSM change (95% CI)	-4.42 (-5.05 to -3.80)	-6.13 (-6.72 to -5.53)
LSM difference vs placebo (95%CI)	**1.70 (0.84 to 2.57)**	
p-value vs. placebo	<0.001	
Minimal clinically important difference	**4**	
MMSE Low/medium tau	N=549	N=573
Mean Baseline (SD)	23.11 (3.64)	22.88 (3.74)
LSM change (95% CI)	-1.61 (-1.89 to -1.33)	-2.09 (-2.36 to -1.81)
LSM difference vs placebo (95%CI)	**0.48 (0.09 to 0.87)**	
p-value vs. placebo	0.02	
Combined group	N=796	N=841
Mean Baseline (SD)	22.52 (3.84)	22.20 (3.90)
LSM change (95% CI)	-2.47 (-2.73 to -2.20)	-2.94 (-3.20 to -2.69)
LSM difference vs placebo (95%CI)	**0.47 (0.10 to 0.84)**	
p-value vs. placebo	0.01	
Minimal clinically important difference	**1 point, MCI; 2 points, mild AD**	

ADAS-cog13: Alzheimer's Disease Assessment Scale-Cognitive subscale; ADCS-iADL: Alzheimer's Disease Cooperative Study‐Activities of Daily Living Scale; Centiloid scale: 100-point scale termed "Centiloid," which is an average value of zero in "high certainty" amyloid negative subjects and an average of 100 in "typical" AD patients (Klunk et al., 2015); CI:

confidence interval; CDR-SB: Clinical Dementia Rating-Sum of Boxes; LSM: least squares mean; MCI: mild cognitive impairment; MMSE: Mini mental state exam; SD: standard deviation.

Safety Considerations

Amyloid-Related Imaging Abnormalities (ARIA) refers to radiographic abnormalities observed with anti-Aß antibodies:

- ARIA-Edema (ARIA-E): vasogenic edema or sulcal effusion
- ARIA-Hemorrhage (ARIA-H): brain microhemorrhages or localized superficial siderosis
- May result from increased cerebrovascular permeability as a consequence of antibody binding to deposited amyloid-beta near cerebral blood vessels

ARIA may be detected in routine MRI screening. If a patient experiences symptoms suggestive of ARIA, clinical evaluation should be performed, including an MRI if indicated.

Note: MRI screening for ARIA in the clinical trials may have caused unblinding, affecting efficacy assessments.

Table 5. Adverse Events with ≥5% of participants [6]

	Donanemab N=853 N (%)	Placebo N=874 N (%)
ARIA-E	205 (24.0)	17 (1.9)
ARIA-H	168 (19.7)	54 (7.4)
Headache	119 (14.0)	86 (9.8)
Fall	114 (13.4)	110 (12.6)
Infusion-related reaction	74 (8.7)	4 (0.5)
Superficial siderosis of CNS	58 (6.8)	10 (1.1)
Dizziness	53 (6.2)	48 (5.5)
Arthralgia	49 (5.7)	42 (4.8)
Death	16 (1.9)	10 (1.1)
Death related to treatment	3 (0.4)	1 (0.1)
Treatment d/c due to AEs	112 (13.1)	38 (4.3)

ARIA: amyloid-related imaging abnormalities; ARIA-E: ARIA-Edema, vasogenic edema or sulcal effusion; ARIA-H: microhemorrhages and hemosiderin deposits; CNS: central nervous system; d/c: discontinuation; AE: adverse event

Table 6. ARIA[6]

ARIA-E by e4 status, N/Total (%)	Donanemab	Placebo
Noncarrier	40/255 (15.7)	2/250 (0.8)
Heterozygous carrier	103/452 (22.8)	9/474 (1.9)
Homozygous carrier	58/143 (40.6)	5/146 (3.4)
Any ARIA, N (%)	314 (36.8)	103 (14.9)
ARIA-E, N (%)	205 (24)	18 (2.1)
Asymptomatic	153 (17.9)	17 (1.9)
Symptomatic	52 (6.1)	1 (0.1)

ARIA-H, N (%)	268 (31.4)	119 (13.6)
Microhemorrhage	229 (26.8)	109 (12.5)
Superficial siderosis	134 (15.7)	26 (3.0)
Intracerebral hemorrhage	3 (0.4)	2 (0.2)

Other warnings / precautions [1]

- Amyloid Related Imaging Abnormalities (ARIA): Enhanced clinical vigilance for ARIA is recommended during the first 24 weeks of treatment. Risk of ARIA, including symptomatic ARIA, was increased in apolipoprotein E e4 homozygotes compared to heterozygotes and noncarriers. The risk of ARIA-E and ARIA-H is increased in 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 discontinued, and appropriate therapy administered as clinically indicated. Consider pre-medication at subsequent dosing with antihistamines, acetaminophen, and/or corticosteroids.

Other Therapeutic Options

Table 7.

Drug	Formulary status	Clinical Guidance/ Indication	Other Considerations
Donanemab	TBD	MCI, Mild AD	Q4wk dosing
Aducanumab	NF	MCI, Mild AD	Discontinued by manufacturer
Lecanemab	NF with CFU	MCI, Mild AD	Real time MUE required via VAMedSAFE

Projected Place in Therapy

- AD is a progressive neurologic disorder affecting approximately 6.7 million Americans over the age of 65. More women than men are affected, and Blacks and Hispanics are at higher risk of developing AD.[8]
- The results from TRAILBLAZER-ALZ-2 support a statistical delay, with donanemab, in the progression of AD in patients with MCI and mild dementia due to AD. However, the difference from placebo in the primary endpoint measure (iADRS, -2.92 to 3.25) did not reach the threshold for a minimal clinically important difference.
- Donanemab effectively removed beta-amyloid. Amyloid clearance was reached in 29.7% of participants at 24 weeks and 76.4% 76 weeks.
- Institute of Clinical and Economical Review (ICER) rated treatment with donanemab in MCI due to AD or mild AD as "Insufficient" (I).[9] However, their analysis only included the Phase 2 study by Mintun et al. The Phase 3 trial by Sims was not included.
- Current formulary agents for the management of AD include the acetylcholinesterase inhibitors (AChEIs) and an NMDA antagonist. These medications may improve measures of global cognitive function in the short term, but the magnitude of change is small. In meta-analyses, the differences in changes between those on AChEIs or memantine compared with those on

placebo ranged from approximately 1 to 2.5 points on the ADAS-Cog-11 and 0.5 to 1 point on the MMSE over 3 months to 3 years of follow up. AChEIs and memantine appeared to increase the likelihood of improving or maintaining patients' global function by 15 percent (for memantine) to 50 percent (for rivastigmine) in the short term (pooled 95% confidence interval range, 0.49 to 2.69).[11] In the TRAILBLAZER-ALZ 2 trial, the adjusted mean differences from placebo on the ADAS-Cog 13 was -1.33. For comparison, the high-dose group of the EMERGE (aducanumab) trial showed a mean difference from placebo on the ADAS-Cog13 of -1.40 and Clarity AD (lecanemab) demonstrated a mean difference from placebo of -1.44.

- Donanemab, like aducanumab and lecanemab, is associated with ARIA-E, ARIA-H, headache, falls and infusion-related reactions. The AChEIs are associated with nausea, diarrhea, and vivid dreams, and memantine is associated with hypertension, dizziness, and GI complaints.
- Patients considered for donanemab will need to have a recent brain magnetic resonance imaging (MRI) prior to initiating treatment, and periodic monitoring with an MRI prior to the 2nd, 3rd, 4th, and 7th, infusions.
- According to the FDA briefing document, there were 19 deaths on donanemab (2.3%) and 16 deaths on placebo (1.9%) that occurred within 76 weeks of randomization.[4] These numbers differ from that reported by Sims et al in Table 5[6].
- The package labeling suggests considering stopping donanemab based on reduction of amyloid plaques to minimal levels on amyloid PET imaging. However, little guidance is provided on when to stop treatment or when it should be restarted.
- In addition to AChEIs and memantine, the monoclonal antibodies (lecanemab and donanemab) offer another class of medications that may be used to manage mild AD. While donanemab effectively removes beta-amyloid, the clinical benefit of doing so is uncertain.

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