Lecanemab-irmb (LEQEMBI)
National Drug Monograph
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

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

- Lecanemab is a humanized IgG1 monoclonal antibody that binds with high affinity to Aβ soluble protofibrils

Indication(s) Under Review in This Document

- Lecanemab is indicated for the treatment of Alzheimer's disease. Treatment should be initiated in patients with mild cognitive impairment or mild dementia stage of disease who have a confirmed presence of Aβ pathology, the population in which treatment was initiated in clinical trials.

Dosage Form(s) Under Review

- Injection: 100 mg/ml to be given as an intravenous (IV) infusion, 10 mg/kg, over an hour, every 2 weeks

Clinical Evidence Summary

Efficacy Considerations

- The efficacy of lecanemab (BAN2401), supporting its FDA approval, was evaluated from industry-sponsored studies, including a phase 2b, dose-finding trial (Study 201, NCT0176311) and an 18-month, multicenter, double-blind, phase 3 trial (Clarity AD, NCT03887455).
- The study populations included patients (who had a positive amyloid PET scan or CSF) with mild cognitive impairment (MCI) due to AD or mild dementia due to AD (NIA-AA criteria, CDR 0.5-1), a Mini-Mental State Exam (MMSE) score between 22-30, and memory impairment [Wechsler Memory Scale IV-Logical Memory (subscale) II] $\geq$1 standard deviation below age-adjusted mean. MCI is associated with minor changes in cognition and short-term memory loss, but no significant impairment in social or occupational functioning. Mild AD is associated with noticeable lapses in memory and possible difficulty with activities of daily living (ADL) but with preserved ability to function independently (Table 1).
- Study 201, involving 854 patients, failed to meet the prespecified clinical endpoint. It did not show a significant difference between lecanemab and placebo using a Bayesian analysis of 12-

month change on the Alzheimer's Disease Composite Score (ADCOMS, primary end point). The primary Bayesian analysis of ADCOMS at week 53 indicated that the lecanemab 10 mg/kg biweekly dosing regimen had a 64% probability of being superior to placebo by 25%, which did not meet the prespecified criterion for success of 80% probability. However, analyses at 18 months showed dose- and time-dependent clearance of amyloid with lecanemab, and the drug was associated with less clinical decline on some measures than placebo.

- Clarity AD enrolled 1795 participants. At baseline, 52% of patients (lecanemab) and 54% (placebo), were taking other AD medication (Table 2).
- The primary outcome was the change from baseline in mean score on the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) at 18 months. 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 mean CDR-SB (primary endpoint) score was 3.2 at baseline. The adjusted least-squares mean change from baseline at 18 months favored lecanemab over placebo (difference, -0.45; 95% confidence interval [CI], -0.67 to -0.23; P<0.001). What constitutes a clinically meaningful change in scores has not been clearly defined. However, Lansdall et al[14] and others [3,13] suggest that the threshold for clinically meaningful decline increases from MCI to moderate-severe AD. Specifically, the minimal clinically important difference (MCID) for CDR-SB in patients with MCI is a 1-point increase and a 2-point increase in score for patients with mild AD, a metric not achieved in the lecanemab study arm (Table 3).
- Secondary outcome measures included the change in amyloid burden on PET, the score on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale; an assessment of the participants' ability to perform activities of daily living (ADAS-cog14; range, 0 to 90; higher scores indicate greater impairment), the Alzheimer's Disease Composite Score (ADCOMS; range, 0 to 1.97; higher scores indicate greater impairment), and the score on the Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale for Mild Cognitive Impairment (ADCSMCI- ADL; range, 0 to 53; lower scores indicate greater impairment).
- Key secondary endpoints of brain amyloid burden, ADAS-cog14 score, ADCOMS, and ADCS-MCI-ADL score are reflected in Table 4. The MCID for ADAS-Cog14 is a change of 2 points for MCI due to AD[14] and $\geq$ 3 points for mild AD[10,15], a metric not met in the lecanemab study group. There are no data on MCID for ADCOMS and ADCS-MCI-ADL.[8] (Table 4).

Table 1. Key Inclusion and Exclusion Criteria for Clarity [16]

Inclusion

- Diagnosis of MCI due to AD (CDR score 0.5) or mild AD (CDR score 0.5-1)
- Memory impairment [Wechsler Memory Scale IV-Logical Memory (subscale) II] >1 standard deviation below age-adjusted mean.
- Positive biomarker for brain amyloid pathology (PET, CSF t-tau/Aβ)
- Aged ≥ 50 and ≤ 90 years
- An MMSE score between 22 and 30
- BMI > 17 and < 35
- If using drugs to treat symptoms related to AD, doses must be stable for at least 12 weeks prior to baseline.

Exclusion

- Any neurological condition (other than AD) that may be a contributing cause of the subject's cognitive impairment
- Transient ischemic attack, stroke, or seizures within 1 year prior to screening
- Any psychiatric diagnosis or symptoms, (e.g., hallucinations, major depression, or delusions) that could interfere with study procedures in the subject.
- Geriatric Depression Scale (GDS) score greater than or equal to 8 at screening.
- Contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants
- Evidence of other clinically significant lesions on brain MRI at screening that could indicate a dementia diagnosis other than AD.
- Other significant pathological findings on brain MRI at Screening, including but not limited to: more than 4 microhemorrhages; a single macro hemorrhage greater than 10 mm at greatest diameter; an area of superficial siderosis; evidence of vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease; space occupying lesions; or brain tumors
- Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study.
- Subjects with a bleeding disorder that is not under adequate control (including a platelet count <50,000 or international normalized ratio [INR] >1.5).
- Have thyroid stimulating hormone above normal range
- Abnormally low serum vitamin B12 levels
- Known to be human immunodeficiency virus (HIV) positive
- Subjects with malignant neoplasms within 3 years of screening
- Answer "yes" to Columbia-Suicide Severity Rating Scale (C-SSRS) suicidal ideation Type 4 or 5, or any suicidal behavior assessment within 6 months before screening, at screening, or at the baseline visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before screening.
- Known or suspected history of drug or alcohol abuse or dependence within 2 years before screening or a positive urine drug test at screening.

Table 2. Baseline Characteristics of Study Participants [6]

Characteristic	Lecanemab N=859	Placebo N=875
Age, years, mean	71.4	71.0
% Female	51.6	53.0
Race/ethnicity, n (%)		
White	655 (76.3)	677 (77.4)
Black	20 (2.3)	24 (2.7)
Asian	147 (17.1)	148 (16.9)
Hispanic	107 (12.5)	108 (12.3)
Other	37 (4.3)	26 (3.0)
Concomitant AD medication (%)	52.0	53.5
ApoE e4 carrier, n (%)	592 (68.9)	600 (68.6)
ApoE e4 heterozygote	456 (53.1)	468 (53.5)
ApoE e4 homozygote	136 (15.8)	132 (15.1)
Global CDR score, n (%)		
0.5	694 (80.8)	706 (80.7)
1	165 (19.2)	169 (19.3)
MMSE score, mean +/- SD	25.5 +/-2.2	25.6 +-2.2
Stage of disease, n (%)		
MCI due to AD	528 (61.5)	544 (62.2)
Mild dementia due to AD	331 (38.5)	331 (37.8)

Table 3. Primary Endpoint – Change from baseline to 18 months in the CDR-SB score[6]

	Lecanemab (N=859)	Placebo (N=875)
Baseline CDR-SB, Mean +/-SD	3.17 +/- 1.34	3.22 +/-1.34
Adjusted mean change	1.21	1.66
Adjusted mean difference vs placebo (95%CI)	**-0.45** (-0.67 to -0.23)	-
p-value vs. placebo	<0.001	-
Minimal clinically important difference	**Change of 1-2 points**	-

CDR-SB: Clinical Dementia Rating-Sum of Boxes; CI: confidence interval; SD: standard deviation; NOTE: baseline CDR-SB scores equate to questionable impairment

Table 4. Secondary Endpoints – Change from baseline to 18 months [6]

Endpoint	Lecanemab (N=859)	Placebo (N=875)
Amyloid burden on PET - centiloids	N=354	N=344
Mean Baseline (>30 considered elevated)	77.92	75.03
Adjusted mean change	-55.48	3.64
Adjusted mean difference vs placebo (95%CI)	-59.12 (-62.64 to -55.60)	
p-value vs. placebo	<0.001	
ADAS-cog14 score	N=854	N=872
Mean Baseline	24.45	24.37
Adjusted mean change	4.14	5.58
Adjusted mean difference vs placebo (95%CI)	-1.44 (-2.27 to -0.61)	
p-value vs. placebo	<0.001	
Minimal clinically important difference	Change of 2 points for MCI due to AD and ≥3 points for mild AD	
ADCOMS	N=857	N=875
Mean Baseline	0.398	0.400
Adjusted mean change	0.164	0.214
Adjusted mean difference vs placebo (95%CI)	-0.050 (-0.074 to -0.027)	
p-value vs. placebo	<0.001	
Minimal clinically important difference	No data	
ADCS-MCI-ADL score	N=783	N=796
Mean Baseline	41.2	40.9
Adjusted mean change	-3.5	-5.5
Adjusted mean difference vs placebo (95%CI)	2.0 (1.2 to 2.8)	

p-value vs. placebo	<0.001	
Minimal clinically important difference	No data	

ADAS-cog14: Alzheimer's Disease Assessment Scale; ADCOMS: Alzheimer's Disease Composite Score; ADCS-ADL-MCI: Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale for Mild Cognitive Impairment; 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)

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 was detected in routine MRI screening. If mild, dosing was continued if asymptomatic, otherwise dosing was suspended. In cases of moderate to severe ARIA dosing was temporarily suspended until ARIA resolution. In patients with severe ARIA-H, dosing was permanently discontinued. Note: MRI screening for ARIA may result in unblinding.

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

	Lecanemab N=898 N (%)	Placebo N=897 N (%)
Infusion related reaction	237 (26.4)	66 (7.4)
ARIA-H with brain microhemorrhage or hemosiderin deposits	126 (14.0)	69 (7.7)
ARIA-E	113 (12.6)	15 (1.7)
Headache	100 (11.1)	73 (8.1)
Fall	93 (10.4)	86 (9.6)
UTI	78 (8.7)	82 (9.1)
Back pain	60 (6.7)	52 (5.8)
Arthralgia	53 (5.9)	62 (6.9)
Superficial siderosis of CNS	50 (5.6)	22 (2.5)
Dizziness	49 (5.5)	46 (5.1)
Diarrhea	48 (5.3)	58 (6.5)
Anxiety	45 (5.0)	38 (4.2)

ARIA: amyloid-related imaging abnormalities; ARIA-E: ARIA-Edema, vasogenic edema or sulcal effusion; UTI: urinary tract infection; CNS: central nervous system

NOTE: After the randomized phase of the trial was completed, two patients receiving open-label lecanemab died due to cerebral hemorrhage. One individual received t-PA and the other received apixaban (Table 6). A third death, determined not related to anticoagulation, has been tied to lecanemab. Scientists tie third clinical trial death to experimental Alzheimer's drug | Science | AAAS

Table 6. Cerebral Macro hemorrhage with Anticoagulant Use in studies 201 and 301.

Study	Placebo n/N (%)	Lecanemab n/N (%)
201 core	0/20 (0%)	0/11 (0%)
201 open-label extension (OLE)	N/A	0/18 (0)
301	0/74 (0%)	2/83 (2.4%)
301 + OLE	N/A	5/140 (3.6%)
301 & OLE deaths	0/74 (0%)	2/140 (1.4%)

Other warnings / precautions [1]

- Amyloid Related Imaging Abnormalities (ARIA): Enhanced clinical vigilance for ARIA is recommended during the first 14 weeks of treatment. Risk of ARIA, including symptomatic ARIA, was increased in apolipoprotein E e4 homozygotes compared to heterozygotes and noncarriers. 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 antihistamine, NSAIDs, or corticosteroids.

Other Therapeutic Options

Table 7.

Drug	Formulary status	Clinical Guidance/ Indication	Other Considerations
Lecanemab	TBD	MCI, Mild AD	CMS petitioned to remove CED
Aducanumab	NF	MCI, Mild AD	CMS Coverage with Evidence Development (CED) clinical trial
Donepezil	F (5mg and 10mg only)	Mild-Severe AD	Off-label use in dementia associated with Parkinson disease, Lewy bodies and vascular dementia
Galantamine	F	Mild-Moderate AD	Off-label use in severe AD and dementia associated with Parkinson disease, Lewy bodies and vascular dementia
Memantine	F	Moderate-Severe AD	Off-label use in dementia associated with Parkinson disease, Lewy bodies, vascular dementia, and prevention of neurocognitive toxicity of whole brain irradiation

Rivastigmine	F (patch only)	Mild-Moderate AD (oral); Mild-Severe AD (patch); Parkinson disease dementia	Off-label use in dementia associated with Lewy bodies and vascular dementia

Projected Place in Therapy

- AD is a progressive neurologic disorder affecting approximately 6 million Americans. More women than men are affected, and African Americans and Hispanics are at higher risk of developing AD.[7]
- The results from CLARITY AD support a statistical delay, with lecanemab, in the progression of AD in patients with MCI and mild AD. However, the difference from placebo in the primary endpoint measure (CDR-SB, -0.45) did not reach the threshold for a minimal clinically important difference.
- Lecanemab effectively removed beta-amyloid.
- Institute of Clinical and Economical Review (ICER) rated treatment with lecanemab in MCI due to AD or mild AD as "Promising but Inconclusive" (P/I).[8]
- 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).[9] In the Clarity AD trial, the adjusted mean differences from placebo on the ADAS-Cog 14 was -1.44. For comparison, the high-dose group of the EMERGE (aducanumab) trial showed a mean difference from placebo on the ADAS-Cog13 of -1.4.
- Lecanemab, like aducanumab 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 lecanemab will need to have a recent (within one year) brain magnetic resonance imaging (MRI) prior to initiating treatment and periodic monitoring with MRI prior to the 5th, 7th, and 14th infusions.
- Two patients receiving open-label lecanemab died due to cerebral hemorrhage. A third death, apparently not related to anticoagulation, has been tied to lecanemab. Additional, long-term safety data are needed.
- In addition to AChEIs and aducanumab, lecanemab is another medication that may be used to manage mild AD. While lecanemab effectively removes beta-amyloid, the clinical benefit of doing so is uncertain.

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