Aducanumab-avwa (ADUHELM)
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

- Aducanumab is a human monoclonal antibody that promotes clearance of beta-amyloid plaques from the brain

Indication(s) Under Review in This Document

- Aducanumab 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, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with aducanumab. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

Dosage Form(s) Under Review

- Injection; 170 mg/1.7ml, 300 mg/3ml. To be given as an intravenous (IV) infusion, 10 mg/kg over 1 hour every 4 weeks

Clinical Evidence Summary

Efficacy Considerations

- The efficacy of aducanumab, supporting its FDA approval, was evaluated in two identical, Phase III randomized clinical trials, ENGAGE (Study 301, Study 2, NCT02477800) and EMERGE (Study 302, Study 1, NCT02484547).
- The trials randomized patients (who had a positive amyloid PET scan) with mild cognitive impairment (MCI) or mild dementia due to Alzheimer's disease (AD) to low or high dose aducanumab, or placebo. MCI is associated with minor changes in cognition and short-term memory loss, mild but detectable functional impairment and 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.

- Patients were initially dosed based on the presence or absence of apolipoprotein e4 (APOE e4) which is a genetic marker for AD risk. Midway through the trials, the trial protocol was amended such that the high-dose group was titrated to 10 mg/kg, regardless of APOE e4 status. In March 2019, ENGAGE and EMERGE were terminated following a prespecified interim analysis for futility (Tables 1,2).
- At baseline, 52% of patients (EMERGE), 56% (ENGAGE), were taking other AD medication.
- Aducanumab removed beta-amyloid in both trials and at both doses, in a dose dependent manner (Table 3). The reduction in beta-amyloid plaques, a biomarker of AD, was used by the FDA as a surrogate endpoint in its decision to provide accelerated approval; however, a valid surrogate endpoint also depends on a meaningful clinical change.
- The primary outcome was the change from baseline in mean score on the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) at week 78. 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 ENGAGE trial failed to show a difference in CDR-SB scores for both the low- and high-dose arms at week 78. However, the EMERGE trial showed a statistically significant difference in the change from baseline in the CDR-SB score in the high-dose arm but not the low-dose arm (Table 4).
- Secondary outcome measures included a cognitive performance evaluation using the Mini-Mental State Exam (MMSE) and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog 13); and an assessment of the participants' ability to perform activities of daily living with the Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (ADSC-ADL-MCI). MMSE scores range from 0 to 30, with higher scores indicating less cognitive impairment. ADAS-Cog 13 scores range from 0 to 85, with higher scores indicating more cognitive impairment and ADCS-ADL-MCI scores range from 0 to 53, with higher scores indicating less deterioration. A clinically meaningful change in the MMSE score is a decline in score of 1 point for MCI and a 2 point decline in mild AD.[3] A clinically relevant change on the ADAS-Cog score is estimated to be a 3-4 point decline.[9] Analysis of the secondary outcome measures is consistent with that observed with the primary endpoints; no difference in low- or high-dose group in the ENGAGE trial, and only high dose was significant in EMERGE trial (Table 5).
- Subsequent analyses of patients who consented to protocol version 4 or higher prior to week 16 (patients who consented by this time had the opportunity to receive all 14 doses of 10 mg/kg according to the protocol amendment) in intent to treat population showed a more favorable outcome on the change in CDR-SB from placebo for low- and high-dose aducanumab. The summary estimate from meta-analysis for low-dose [-0.39 (-0.76, -0.01)] and high-dose [-0.51 (-0.88, -0.13)] were significant ($p<0.05$, Table 6).[7] What constitutes a clinically meaningful change in scores has not been clearly defined. However, Andrews et al suggests that the threshold for clinically meaningful decline increases from MCI to moderate-severe AD. Specifically, the minimal clinically important difference for CDR-SB in patients with MCI is a 1-point increase and a 2-point increase in score for patients with mild AD.[3]

- The Institute of Clinical and Economical Review (ICER) states that "the evidence is insufficient to conclude that the clinical benefits of aducanumab outweigh its harms or, indeed, that it reduces progression of AD."[7]

Table 1. Study Overview

Trial	Dosing Schedule	Treatment Arms (n)	APOE e4 status, n (%)	Clinical Stage, n (%)
ENGAGE	Dosing Protocol V 1-3 Low-dose APOE e4+, 3 mg/kg Low-dose APOE e4-, 6 mg/kg High-dose APOE e4+, 6 mg/kg High-dose APOE e4-, 10 mg/kg	Low-dose ADU (n=547) High-dose ADU (n=555) Placebo (n=545)	APOE e4+: 1145 (69.5) APOE e4-: 499 (30.3)	MCI: 1325 (80.4) Mild AD: 322 (19.6)
EMERGE	Dosing Protocol V 4-6 Low dose – unchanged High-dose=10 mg/kg regardless of APOE e4 status	Low-dose ADU (n=543) High-dose ADU (n=547) Placebo (n=548)	APOE e4+: 1095 (66.8) APOE e4-: 537 (32.8)	MCI: 1336 (81.6) Mild AD: 302 (18.4)

Table 2. Key Inclusion and Exclusion Criteria for EMERGE and ENGAGE[4]

Inclusion

- Must meet all clinical criteria for MCI due to AD or mild AD
- CDR-Global Score of 0.5
- Objective evidence of cognitive impairment at screening
- An MMSE score between 24 and 30 (inclusive)
- Must have a positive amyloid PET scan
- Must consent to ApoE genotyping
- If using drugs to treat symptoms related to AD, doses must be stable for at least 8 weeks prior to screening visit 1

Exclusion

- Any medical or neurological condition (other than AD) that may be a contributing cause of the subject's cognitive impairment
- Clinically significant unstable psychiatric illness within 6 months prior to screening
- Transient ischemic attack or stroke or any unexplained loss of consciousness within 1 year prior to screening
- Brain MRI performed at screening that shows evidence of any of following: acute or sub-acute hemorrhage, prior microhemorrhage or prior subarachnoid hemorrhage (unless finding

is not due to an underlying structural or vascular hemorrhage), ≥4 microhemorrhages, cortical infarct, >1 lacunar infarct, superficial siderosis or history of diffuse white matter disease
- Contraindications to having a brain MRI or PET scan
- History of bleeding disorder
- Use of medications with platelet anti-aggregant or anti-coagulant properties (unless aspirin at ≤325 mg daily)
- Participation in any active immunotherapy study targeting Aβ, any passive immunotherapy study targeting Aβ within 12 months of screening or any study with purported disease-modifying effect in AD within 12 months of screening unless documentation of receipt of placebo

Table 3 Biomarker Result of aducanumab in EMERGE[1]

Biomarker endpoint at week 78	High dose aducanumab	Placebo
Amyloid beta PET composite SUVR	N=170	N=159
Mean baseline	1.383	1.375
Change from baseline Difference from placebo	-0.264 -0.278 (p<0.0001)	0.014
Amyloid beta PET centiloid	N=170	N=159
Mean baseline	85.3	83.5
Change from baseline Difference from placebo	-60.8 (-71%) -64.2 (p<0.0001)	3.4

SUVR: Standard Uptake Value Ratio; 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)

Table 4. Primary Endpoint - CDR-SB at Week 78, ITT Population[4,5]

	ENGAGE			EMERGE		
	Placebo (n=545)	**ADU Low Dose (n=547)**	**ADU High Dose (n=555)**	**Placebo (548)**	**ADU Low Dose (n=543)**	**ADU High Dose (n=547)**
Baseline CDR-SB, Mean	2.40	2.43	2.40	2.47	2.46	2.51
Adjusted Mean Change from Baseline at Week 78 (95% CI)	1.56 (1.23, 1.77)	1.38 (1.16, 1.59)	1.59 (1.37, 1.81)	1.74 (1.51, 1.96)	1.47 (1.25, 1.70)	1.35 (1.12, 1.57)
Difference vs. Placebo (95% CI)	--	-0.18 (-0.47, 0.11)	0.03 (-0.26, 0.33)	--	-0.26 (-0.57, 0.04)	-0.39* (-0.69, -0.09)
% Difference vs. Placebo	--	-12%	2%	--	-15%	-22%
p-value (vs. Placebo)	--	0.2250	0.8330	--	0.0901	0.0120

ADU: aducanumab, CDR-SB: Clinical Dementia Rating-Sum of Boxes, CI: confidence interval, ITT: intention-to-treat
*p<0.05. NOTE: baseline CDR-SB scores equate to questionable impairment

Table 5. Secondary Endpoints

	ENGAGE[4,5]			EMERGE[4,5]		
	Placebo Decline	Difference vs. Placebo (p-value)		Placebo Decline	Difference vs. Placebo (p-value)	
		Low Dose	High Dose		Low Dose	High Dose
MMSE	-3.5	0.2 (0.48)	-0.1 (0.81)	-3.3	-0.1 (0.76)	0.6 (0.05)
ADAS-Cog 13	5.14	-0.58 (0.25)	-0.59 (0.26)	5.16	-0.7 (0.20)	-1.4 (0.01)
ADCS-ADL-MCI	-3.8	0.7 (0.12)	0.7 (0.15)	-4.3	0.7 (0.15)	1.7 (0.0006)

ADAS-Cog 13: Alzheimer's Disease Assessment Scale-Cognitive Subscale, ADCS-ADL-MCI: Alzheimer's Disease Cooperative Study Scale for Activities of Daily Living in Mild Cognitive Impairment, MMSE: Mini-Mental State Exam

Table 6. Post-Hoc Analysis of CDR-SB at Week 78 for Post-PV4 population

	ENGAGE			EMERGE		
	Placebo (n=247)	ADU Low Dose (n=261)	ADU High Dose (n=282)	Placebo (304)	ADU Low Dose (n=295)	ADU High Dose (n=288)
Baseline CDR-SB, Mean	2.40	2.43	2.40	2.47	2.46	2.51
Mean Change from Baseline at Week 78	1.79	1.44	1.31	1.76	1.34	1.23
Difference vs. Placebo (95% CI)	--	-0.35 (-0.88, -0.18)	-0.48 (-1.02, 0.06)	--	-0.42 (-0.94, 0.10)	-0.53 (-1.05, -0.02)
% Difference vs. Placebo	--	-20%	-27%	--	-24%	-30%
p-value (vs. Placebo)	--	Ns	Ns	--	Ns	P<0.05

ADU: aducanumab, CDR-SB: Clinical Dementia Rating-Sum of Boxes, CI: confidence interval, Post-PV4: protocol version 4 or higher. NOTE: baseline CDR-SB scores equate to questionable impairment

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

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 have resulting in unblinding

Table 7. Adverse Events with ≥5% Incidence in Aducanumab 10 mg/kg ≥2% Difference from Placebo [Studies 301 (ENGAGE) and 302 (EMERGE) Placebo-Controlled Period]

	Placebo N=1087 N %	ADU 10 mg/kg N=1033 N %
ARIA-E e4 + e4 – symptomatic asymptomatic	29 (2.7) 16/742 (2.2) 13/334 (3.9) 3 (10.3) 26 (89.7)	362 (35) 290/674 (43) 72/355 (20.3) 94 (26) 268 (74)
Headache	165 (15.2)	212 (20.5)
ARIA-H Brain microhemorrhage	71 (6.5)	197 (19.1)
Fall	128 (11.8)	155 (15.0)
ARIA-H Superficial siderosis	24 (2.2)	151 (14.6)
Diarrhea	74 (6.8)	92 (8.9)
Confusion/delirium/disorientation/ Altered mental status	4%	8%

Other warnings / precautions:

- Hypersensitivity reactions
- Dizziness/vertigo
- Visual disturbance
- Nausea

Other Therapeutic Options

Table 8.

Drug	Formulary status	Clinical Guidance/ Indication	Other Considerations
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

Current formulary agents (list above) 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).[8] For comparison, the high-dose group of the EMERGE trial showed a differences from placebo on the ADAS-Cog 13 of 1.4 and 0.6 for the MMSE.

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.[6] Safe and effective agents that halt or delay the progression of AD are clearly needed. Aducanumab-avwa is a human monoclonal antibody that promotes clearance of beta-amyloid plaques from the brain and is indicated for the treatment of AD, specifically, in patients with mild cognitive impairment or mild dementia stage of disease.
- While VA PBM acknowledges the recent FDA decision on aducanumab-avwa, given the lack of evidence of a robust and meaningful clinical benefit and the known safety signal, we **recommend against** offering this agent to patients with Alzheimer's dementia (mild or otherwise) or mild cognitive impairment. However, recognizing that there is an accelerated

FDA approval, we also recommend that if it is to be used by exception then it should be utilized only in highly selected patients by experts and centers that have the necessary diagnostic and management expertise— and only by those with the needed resources for close monitoring to assure safety. As such, any use should be governed by stringent regulation, and safety and appropriateness of use monitored real time by VAMedSAFE.

- VA PBM recommends that the use of aducanumab-avwa be governed by ALL of the following safety standards:
    - The prescriber is a VA (not VA Community Care) neurologist, psychiatrist or geriatrician who specializes in treating dementia.
    - The patient has a signed written informed consent on file.
    - The patient has a recent brain MRI, meets clinical criteria for mild cognitive impairment (MCI) with Alzheimer's pathology or mild AD, and has an amyloid PET imaging that is consistent with Alzheimer's pathology, and/or CSF analysis consistent with Alzheimer's disease (low amyloid β42).
    - An ApoE genotype has been obtained and documented in the patient's chart to guide informed decision making.
    - The patient has a Clinical Dementia Rating (CDR) Global score of 0.5 or Functional Assessment Staging Test (FAST) Stage score of 2 or 3.
    - There is a documented Mini-Mental State Examination (MMSE) score $\geq$ 24 or equivalent (e.g. Saint Louis University Mental Status (SLUMS)) score).
    - Neuroradiology must be available to review serial MRI scans, either at site, or through National Teleradiology. In case there is MRI evidence of amyloid related imaging abnormalities (ARIA), a process should be in place before starting therapy to ensure the provider and pharmacy are notified to hold the infusion until the ordering physician can assess the patient and decide whether to stop treatment.
    - Dosage, administration, monitoring, and discontinuation of aducanumab-avwa therapy adhere to those recommended in the prescribing information.
- VA PBM recommends that aducanumab-avwa NOT be used if the patient has any of the following conditions:
    - Any condition other than Alzheimer's disease that may be a contributing cause of the patient's cognitive impairment (e.g. TBI, PTSD).
    - A contraindication to having a brain MRI and PET scan.
    - A screening brain MRI that shows evidence of any of the following: acute or sub-acute hemorrhage, prior microhemorrhage or prior subarachnoid hemorrhage, ≥4 microhemorrhages, cortical infarct, >1 lacunar infarct, superficial siderosis or history of diffuse white matter disease.
    - The patient has a history of bleeding disorder or is using medications with anti-platelet or anti-coagulant properties (except aspirin at < 325 mg daily),
    - The patient has uncontrolled hypertension or history of unstable angina, myocardial infarction, chronic heart failure or clinically significant cardiac conduction abnormalities.
    - The patient has experienced a transient ischemic attack or stroke or any unexplained loss of consciousness within the past year.

References

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