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Drug Class Update with New Drug Evaluation: Alzheimer's Disease, Targeted Therapies

Date of Review: December 2024

Date of Last Review: October 2023
Dates of Literature Search: 10/1/2023 – 09/26/2024
Brand Name (Manufacturer): Kisunla (Eli Lilly and Company)
Dossier Received: yes

Generic Name: donanemab-azbt

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
To review new evidence for efficacy and harms of the new monoclonal antibody agent, donanemab, in the treatment of early Alzheimer's dementia (AD). This review will also evaluate new evidence for other agents approved to treat AD and update prior authorization criteria as needed.

Plain Language Summary:
- This review looks at new evidence for medicines that are used for Alzheimer's disease.
- Alzheimer's disease (AD) is a condition that makes it difficult for a person think, remember, speak, and complete daily activities of life.
- About 1-2% of people over the age of 65 years have AD, but it becomes more common with increasing age.
- There is no cure for AD at this time. There are some medicines called acetylcholinesterase inhibitors (ACHEIs) that increase levels of chemical messengers in the brain. These medicines may help people with AD think or speak more clearly or help to take better care of themselves. However, these medicines may only have a small benefit and usually work for only a short amount of time (6 to 9 months). These medicines may upset the stomach or cause weight loss.
- A new medicine, donanemab (KISUNLA), is used to treat patients with mild AD to help clear the brain of harmful proteins that might worsen AD. However, patients taking donanemab may have a high risk of developing brain swelling or brain bleeding side-effects when using this drug, so treatment must be closely watched. There is not good evidence that these types of medicines help a patient think more clearly, improve their memory, or help them do daily activities.
- The Drug Use Research and Management group recommends that donanemab be available for use under the Oregon Health Plan fee-for-service program if the prescriber can explain that it is needed, and that it will likely be safe and work for their patient. This process is called prior authorization.

Research Questions:
1. What is the efficacy of donanemab compared to placebo or currently available treatments for Alzheimer's disease (AD)?
2. What is the safety of donanemab compared to placebo or currently available treatments for AD?

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3. Are there any subgroups (based on age, gender, race, ethnicity, socioeconomic status, comorbidities, disease duration or severity) that would particularly benefit or be harmed by treatment with a specific agent for AD?

Conclusions:

- Since the last class update, there is no new direct comparative evidence published for drug therapies in people with AD. The FDA has approved a new monoclonal antibody, donanemab, indicated for the treatment of AD in patients with mild cognitive impairment or mild dementia.[1,2]
- One phase 3 randomized controlled trial (RCT) reported that donanemab treatment over 76 weeks resulted in a modest but statistically significant change from baseline in the integrated Alzheimer's Disease Rating Scale (iADRS) compared to placebo in patients with low/medium tau levels (mean difference [MD] 3.25 less decline [-35%], p<0.001) and also in the combined population (MD 2.92 less decline [-22%], p<0.001) of patients with early AD.[1-3] In relation to the 144-point scale range, a 3-point change compared to placebo did not meet the minimum clinically important difference (MCID) reported in literature [-5 points (patients with mild cognitive impairment (MCI); -9 points (Mild AD)].[4] For secondary outcomes, there were statistically significant changes that favored donanemab compared to placebo in the sum of boxes of the Clinical Dementia Rating Scale (CDR-SB) (combined: MD −0.67 [95% CI −0.92 to −0.43]; p<0.001).[1-3] Based on the 18-point scale, the changes compared to placebo did not meet the MCID reported in literature [1 point (MCI); 2 points (Mild, and Moderate to Severe AD)].[4] There were statistically significant changes that favored donanemab over placebo in the Alzheimer Disease Cooperative Study—Instrumental Activities of Daily Living (ADCS-iADL) combined: MD 1.70 [95% CI 0.84 to 2.57]; p<0.001; MCID not reported), in the Alzheimer's Disease Assessment Scale-Cognition-13 (ADAS-Cog13) (combined: MD −1.33 [95% CI −2.09 to −0.57]; p<0.001; MCID = 2 to 3 points), and in the Mini-Mental State Examination (MMSE)(combined: MD 0.47 [95% CI 0.10 to 0.84], p=0.01; MCID 1 to 2 points) but the clinical significance of the modest changes are unclear.[1-3]
- There is insufficient evidence to evaluate impact of donanemab on functional and cognitive outcomes in patients at the early stages of AD. Available evidence is limited by risk for performance, detection, attrition, and reporting bias, and by lack of evaluation of patients with advanced AD, with low levels of amyloid-beta (AB) plaque, or in those who developed amyloid related imaging abnormalities (ARIA) while on therapy.[1-3]
- The FDA issued a safety alert for the amyloid-lowering therapy lecanemab due to the possibility of serious hypersensitivity reactions including angioedema and anaphylaxis.[5] There is also a boxed warning that lecanemab can cause ARIA and rare but serious and life-threatening events such as intracerebral hemorrhage greater than 1 cm.[5]
- The commercialization and sale of aducanumab (Aduhelm™) was recently halted by the manufacturer and will no longer be available after November 1, 2024.

Recommendations:

- Designate donanemab as non-preferred on the preferred-drug list (PDL).
- Implement prior authorization (PA) criteria for donanemab and update existing criteria as proposed (**Appendix 5**).

Summary of Prior Reviews and Current Policy

- Therapies Food and Drug Administration (FDA)-approved for the treatment of AD were previously reviewed by the Pharmacy and Therapeutics (P&T) Committee in October 2023.
- There was low to moderate quality evidence that acetylcholinesterase inhibitors (ACHEIs) improved outcomes of cognition in patients with mild to moderate AD compared to placebo but insufficient evidence that one agent was more efficacious or safer than another. ACHEIs and memantine also demonstrated modest but persistent improvements in cognition, activities of daily living, and behavior in patients with moderate to severe AD. In patients with severe AD, there was low-quality evidence that donepezil improved outcomes of function. The overall magnitude of benefit with ACHEIs for improvements in cognition

and function was relatively small. There was low to moderate quality evidence that discontinuation of an AChEI at 12 months (compared to continuing treatment) likely resulted in greater functional impairment and worse cognitive function but little to no change in neuropsychiatric status.

- None of the approved medications had been shown to stop or reverse the underlying process of AD or have any impact on important clinical outcomes such as mortality, disability, or institutionalization in patients with AD.
- There was insufficient evidence that use of the amyloid-reducing immunotherapy agents aducanumab and lecanemab for the treatment of patients with mild AD has clinically meaningful impact on symptoms, cognitive or functional improvement, quality of life, or disease progression based on a review of evidence presented to the P&T committee in October 2023.
- Amyloid-reducing immunotherapy resulted in an increased incidence of ARIA including brain microhemorrhage and edema compared to placebo. There was insufficient evidence to verify long-term safety of lecanemab or aducanumab, which may be a concern in patients with pre-existing risk factors for bleeding, including concomitant medications that could increase the risk for bleeding. Patients with AD who were homozygotes for the Apolipoprotein E4 (ApoE4) genotype had a greater risk of ARIA compared to heterozygotes and noncarriers when treated with either aducanumab or lecanemab. No comparative efficacy or safety data were available for lecanemab versus other agents used to treat AD.

Background:

Alzheimer's disease is a progressive neurodegenerative condition of memory impairment that primarily affects people with advanced age.[6] Besides memory, AD may impact language, cognition, reasoning skills, social functioning, and activities of daily living.[6] AD is a complex disorder that may be the result of numerous factors such as genetics, environmental stimuli, age, and education.[6] Generally, AD is associated with poor coordination and muscle function, a decline in visual-spatial perception, personality changes, and an incapability of autonomous self-care.[6] Dementia due to AD accounts for 60-80% of all dementia cases.[6] The prevalence of AD appears to increase dramatically with age.[6,7] The percentage of people with AD is around 5% for ages 65 to 74 years but increases to almost 14% for those aged 75 to 84 years.[6,7] By 85 years of age and older, around one-third of the population is estimated to have some form of AD.[6,7] Currently in the United States, an estimated 6 million people aged 65 or older have AD and it is projected that by 2050 the number may surge to more than 13 million.[7] The evidence whether the incidence of AD differs among men and women is inconclusive, but there is some data to suggest a higher incidence rate among Black/African Americans and Hispanic/Latino persons than other racial or ethnic groups.[6]

Physiologic amounts of amyloid-beta (Aβ) peptide have been shown to enhance memory while tau protein appears to have an important role in neuronal microtubule assembly.[8-10] However, dysregulation and accumulation of excess Aβ plaques along with aggregation of intracellular neurofibrillary tangles of tau protein have been linked to the potential development of AD.[8-11] High levels of amyloid-beta increases glycogen synthase kinases that phosphorylate tau protein.[8,10] It has been hypothesized that as tau is phosphorylated, it leads to neurofibrillary tangle (NFT) formation, followed by synapse degradation and disruption of neuron signaling, and eventual neuronal destruction and death.[8,12] Whether tau tangle pathology precedes Aβ plaque formation is still under investigation.[8,9,11] A direct correlation between mean plaque count and cognitive performance has not been conclusively demonstrated.[8] Regardless of pathology, neuronal damage results in widespread neurotransmitter deficiencies including those involved in the cholinergic pathway.[13-15] With less acetylcholine released from presynaptic neurons, the availability of neurotransmitters such as serotonin and norepinephrine involved in memory and mood are hindered, and AD symptoms worsen.[13-15]

There have been several factors identified that may increase risk of AD but the exact etiology is unknown.[7,16] Besides advanced age, genetics and familial history of dementia are thought to have a role in the development of AD.[7,16] Among the roughly 30 genes linked to AD, the ε4 allele of the Apolipoprotein E gene (ApoE4) has been one of the strongest risk factors.[7,17] Although estimates vary between studies and ethnicities, the ApoE4 allele is often present in more than

50% of AD patients but found in only about 15% of healthy older controls.[8,17] Several other risk factors such as previous head trauma, vascular disease, infections, and environmental pollutants have also been reported to increase the risk of AD but studies are inconclusive.[7,16,18-23]. Modifiable risk factors for AD may include low education level, diabetes mellitus, hypertension, and a sedentary lifestyle.[24-26] Alzheimer's dementia generally has a slow onset and progresses gradually over many months or years.[27]

Apart from the gold standard of post-mortem brain autopsy, the diagnosis of AD often requires a detailed review of clinical findings, medical history, and brain imaging.[6,7,27] Evaluation involves ascertainment of medical history from the patient and family member (or caregiver) along with a cognitive and neurologic examination.[7,27,28] The clinical spectrum of AD ranges from asymptomatic to severe impairment.[6,7,27,28] Early disease without symptoms may be characterized as preclinical AD.[6,7,27,28] As neuronal injury ensues, there may be subtle decline in memory, organization, and mood where the patient would be diagnosed with mild cognitive impairment (MCI).[7] In patients with MCI, slight cognitive changes and short-term memory loss are evident, but there is generally little to no substantial impairment of social function or activities of daily living (ADL).[24,25] When changes in personality, speech, and cognition occur that result in functional impairment, a clinical diagnosis of AD is often made.[24,25] AD may be classified as mild, moderate, or severe depending upon the extent that cognitive decline interferes with ADLs.[27] Early-onset AD (EOAD) is rare and generally manifests before 65 years of age.[7] Late-onset AD (LOAD) affects most (greater than 95%) people with AD and typically occurs after 65 years of age.[7] Attempts to screen for AD and related dementia have been unable to show a positive impact on disease prevention or in measures of health-related quality of life.[29,30]

A variety of brain imaging techniques are available to help evaluate suspected AD.[31-34] Classic magnetic resonance imaging (MRI) is useful in detection of low oxygen levels and reduced brain blood flow commonly observed in patients with AD.[33,34] Structural imaging observed through MRI may also reveal hippocampal atrophy which, although not specific to AD, can contribute to diagnostic accuracy.[35] Aβ plaques and NFTs are easily visible with Positron Emission Tomography (PET) neuroimaging.[32-34] PET scans help reveal glucose metabolism in the brain and may also be useful to establish biomarkers of amyloid burden in the progression of AD but not disease severity.[32,33,36] The standardized uptake value ratio (SUVR) is a method to quantify the degree of radioactive tracer uptake in the subject's brain.[37] For imaging with amyloid and tau, SUVR is commonly calculated using the unaffected cerebellum as a reference.[37] Cerebrospinal fluid total tau (T-tau), phosphorylated tau (P-tau), and beta amyloid 42 (Aβ42) have been used as possible biomarkers to detect neuronal degeneration in patients with AD.[31,38,39] Changes in brain amyloid may be measured by PET and converted into a Centiloid scale for comparison of data (100 points possible; 0=healthy, high certainty amyloid negative; 100=typical of AD).[39,40] Use of biomarkers for routine diagnostic purposes is not routinely recommended but supports tracking the molecular and degenerative process of AD.[41]

With no known cure for AD, treatment involves symptom management and strategies to reduce long-term clinical decline.[7] A multifactorial approach generally involves nonpharmacologic and behavioral interventions as well as pharmacotherapy.[7] Current FDA-approved therapies for AD include ACHEIs (e.g. donepezil, galantamine, rivastigmine), the N-methyl-D-aspartate (NMDA) antagonist memantine, and human monoclonal antibodies.[27,29,42] There is reduced acetylcholine synthesis and impaired cholinergic function in patients with AD.[7] ACHEIs increase acetylcholine in the central nervous system via suppression of the metabolizing enzyme acetylcholinesterase.[27] ACHEIs are generally used as first-line therapy in mild to moderate dementia and typically result in modest improvements in cognition, psychiatric symptoms, and ability to perform ADLs.[27,43,44] Memantine blocks the excitatory effects of glutamate by the preferential binding to NMDA receptor channels to facilitate synaptic transmission, neuronal growth and differentiation.[27] Memantine may be used as monotherapy in people with moderate AD who are intolerant or have contraindications to ACHEI therapy, or it may be used alone or in combination with ACHEI in patients with severe AD.[27,38] The newer monoclonal antibodies are approved for mild AD and mostly target the aggregated forms of amyloid beta plaques which includes

soluble oligomers and insoluble fibrils.[45] Widespread use of monoclonal antibodies in patients with AD has been limited likely due to modest short-term effects, high cost, special requirements for drug administration, and safety monitoring. Overall, AChEIs, NMDA antagonists, and monoclonal antibodies have reported only modest treatment effects in different stages of AD.[27] The oral and topical FDA-approved agents for AD along with their dosing and individual properties are listed in **Table 1**.

Table 1. FDA-Approved Pharmacologic Treatments for Dementia Attributed to Alzheimer Disease [2,27,40]

Drug Class	Generic Name	Brand Name	Typical Dose/Route/Frequency	FDA Approved AD Indication	Advantages	Safety Concerns
AChEIs	Donepezil	Aricept™, Aricept ODT™	5 mg or 10 mg orally once daily	Mild to Moderate	Prescriber familiarity; generic, orally disintegrating tablet available	Nausea, vomiting, loss of appetite, increased frequency of bowel movements, vivid dreams, insomnia; use with caution in patients with peptic ulcer disease, respiratory disease, seizure disorder, and urinary tract obstruction; contraindicated in patients with bradycardia
			10 mg or 23 mg orally once daily	Moderate to Severe		
	Galantamine	Razadyne™	4 mg orally twice daily	Mild to Moderate	Solution and generic formulation available	
	Rivastigmine	Exelon™	1.5 mg orally twice daily Max dose 6 mg orally twice daily	Mild to Moderate	Patch and generic formulation available	
NMDA Antagonist	Memantine	Namenda™	5 mg orally once daily up to target max 10 mg orally twice daily	Moderate to Severe	May use as monotherapy or in combination with AChEI; generic formulation available	Headache, constipation, confusion, and dizziness; use with caution in patients with cardiovascular disease, seizure disorder, and severe hepatic and renal impairment
		Namenda XR™	7 mg orally once daily up to target max 28 mg once daily	Moderate to Severe	May use as monotherapy or in combination with AChEI	
			If stabilized on donepezil 10 mg and NOT on memantine:	Moderate to Severe	Combination for reduced pill burden	All of the above

ACHEIs/NMDA Antagonist Combinations	Memantine + Donepezil	Namzaric™	Memantine ER 7 mg/donepezil 10 mg once daily in the evening up to target memantine ER 28 mg/ donepezil 10 mg once daily			
Monoclonal Antibodies	Donanemab	Kisunla™	700 mg IV once every 4 weeks x 3 doses then 1400 mg IV every 4 weeks	Mild	Unknown	ARIA including brain edema and microhemorrhage; cerebral hemorrhage; seizures
	Lecanemab	Leqembe™	10 mg/kg IV once every 2 weeks			
Abbreviations: ACHEI=acetylcholinesterase inhibitor; AD=Alzheimer's dementia; ARIA=Amyloid-related imaging abnormalities; ER=extended release; FDA = Food and Drug Administration; max =maximum; kg=kilogram; mg=milligram; ODT=orally disintegrating tablet; XR = extended release						

Much of contemporary AD drug therapy research has focused on immunotherapy targeted at accumulation of beta amyloid plaques in an attempt to reduce neuronal toxicity and possibly improve synaptic function.[10] Several monoclonal antibodies (MABs) have been developed to either decrease Aβ production, hinder Aβ aggregation, or increase Aβ clearance.[9,10] However, some researchers have questioned the validity of the amyloid hypothesis due to variability of amyloid levels that correlate with AD severity and the limitations of PET tracers.[46] None of the amyloid-lowering therapies have been able to demonstrate changes in amyloid levels can produce a lasting, perceptible symptomatic benefit in slowing AD progression.[10] While the clinical benefit may be unclear, anti-amyloid therapies have known safety risks termed ARIA.[1,47,48] Amyloid related imaging abnormalities are thought to be a result of amyloid deposit removal alongside cerebral arteries which cause vessel leakage and an immune response that can last weeks to months after therapy is stopped.[49] ARIA may be observed in patients who have undergone a MAB infusion which leads to anti-Aβ autoantibody development in the CSF.[1,47,48] ARIA findings via MRI may reveal brain swelling and edema (ARIA-E) or hemorrhage (ARIA-H).[1,47,50] ARIA may present with headache, confusion, visual changes and gait difficulty usually observed between the first and third therapy infusion.[50] Serious ARIA symptoms may include seizures, encephalopathy, stupor, and focal neurologic deficits.[50] For patients with moderate or severe ARIA detected via imaging or who develop symptoms, anti-amyloid MAB therapy should be suspended and monitored closely until ARIA-E resolves or ARIA-H stabilizes.[2,40,42] Not all people with AD develop ARIA after amyloid modifying therapy, but a number of drug trials have suggested that side effect profiles may not only differ between various agents, but also whether patients are ApoE4 carriers or non-carriers.[17,40] In studies of patients treated with the anti–β-amyloid therapies aducanumab, lecanemab, and donanemab, carriers of the ApoE4 genotype had a much greater frequency of ARIA (particularly at higher doses) than non-carriers, and the rates were even higher for ApoE4 homozygotes than heterozygotes.[2,40,51] The risk of ARIA for these agents, notably for those with the ApoE4 genotype, is listed as a warning and precaution in the FDA labeling.[2,51,52] There have also been recent reports of amyloid modifying therapies resulting in significant acceleration of ventricular enlargement in the brain which has been associated with decreased cognitive function and hypothesized may lead to worsening neurodegeneration.[53] Whether brain volume changes are related to risk of ARIA, cognitive/noncognitive outcomes, or other clinical factors has not been elucidated.[53] The FDA's Centre for Drug Evaluation and Research listed changes in volume to brain structures as a key

pharmacodynamic end point in the clinical review of aducanumab.[54] The commercialization and sale of aducanumab (Aduhelm™) was recently halted by the manufacturer and will no longer be available after November 1, 2024.[55]

Clinically important outcomes in AD include mortality, cognitive function, quality of life/independence, functional performance in ADLs, behavioral disturbances, and serious adverse events.[56] Several exams and scales have been used to monitor AD progression and to assess the effectiveness of clinical interventions in AD treatment. Due to the progressive nature and highly variable range of symptoms in AD, clinicians have found it difficult to establish and agree upon thresholds for MCIDs in many AD therapy outcomes.[25] The Alzheimer's Disease Assessment Scale-Cognition (ADAS-Cog) is a validated tool for assessment of cognitive and non-cognitive behaviors in AD.[1,57] The ADAS-Cog consist of subject-completed tests and observer assessments of key items such as memory, orientation, language, and critical thinking.[57] The ADAS-Cog11 scale has a range of 0 to 70 with higher scores indicative of greater severity of disease (MCID = 3 points).[57] The 23-item Alzheimer's Disease Cooperative Study—Activities of Daily Living (ADCS-ADL) instrument is a rater-administered questionnaire completed by the patient's caregiver (range from 0 to 78; higher score indicates less severe disease; MCID not defined).[58] Some studies have used modified versions of the ADCS-ADL in an effort to focus on a different stage or specific symptoms of AD.[3] For example, the ADCS —Instrumental ADL (ADCS-iADL) has been modified from the full assessment tool and is comprised of fewer items and a decreased a score range of 0 to 59 (lower scores indicative of more severe disease).[3] There is no data on MCID for the ADCS-iADL so it is difficult to determine whether the outcomes measured by this instrument are clinically meaningful.

The integrated Alzheimer's Disease Rating Scale (iADRS) is a composite measure of the ADAS-Cog 13 and ADCS-iADL (score range 0 to 144, lower scores indicative of greater disease severity).[1] The iADRS was developed to assess function and cognition in patients at the early stages of the AD.[59] However, the clinical utility of the iADRS as a standalone tool to assess the effects of a drug intervention has been questioned.[1] In its initial review of donanemab, the FDA did not agree that a statistically significant treatment effect on the iADRS was acceptable as a primary efficacy outcome measure unless its two components (ADAS-Cog13 and ADCS-iADL) also demonstrated statistically significant findings.[1] Some studies that have used the iADRS have reported the MCID to be -9 points in patients with mild AD and -5 points in patients with MCI, however, the drugs studied were not approved for use in AD.[4] Some studies have used the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) to measure cognitive and functional impairment in AD.[54] The CDR-SB assesses three domains of cognition (memory, orientation, judgment/problem solving) and three domains of function (community affairs, home/hobbies, personal care) using semi-controlled interviews with the patient and a reliable companion or informant.[54,60] A qualified rater uses the interview data and clinical judgment to assign scores for each domain.[54,60] The CDR-SB score has a range from 0 (normal) to 18 (severe dementia).[54,60] The FDA has accepted the CDR-SB as a valid primary endpoint for clinical trials in patients with early AD due to its psychometric properties and its ability to assess both cognitive and functional disability.[54] An increase of 2-points on the CDR-SB was found to be clinically significant in mild through severe AD and an increase of 1 point was clinically significant in MCI.[60]

Although not specific to AD, the MMSE is also a commonly used scale to assess cognitive impairment in AD (30 points possible, higher indicates less severe disease, MCID defined as 1 to 3 points) which includes multiple areas (e.g. orientation to time and place, registration, attention/calculation, recall, language, and visual construction).[61,62] The MMSE has a range from 0 to 30 points possible and scoring is grouped into levels of severity based on cognitive impairment ($\geq$25 = normal cognition; 21-24 = mild AD; 11-20 = moderate AD; and 10 or less = severe dementia).[61-63] Factors such as education level may influence MMSE scoring.[61-63] Although some studies in patients with mild AD or MCI have reported MCID thresholds for the MMSE between -1 to -2 points, a recent Cochrane review did not find any evidence to support the MMSE as a stand-alone test for early prediction of dementia development in people with mild cognitive impairments (MCI).[62] A summary of the different tools used to assess outcomes in recent clinical trials of patients with mild AD are listed in **Table 2**.

Table 2. Select Cognitive Assessment Tools used in Early Alzheimer's Disease [1,3,4,60]

Assessment Tool	Scale Range	MCID	Comments
ADAS-Cog	0 to 70 (higher score = worse symptoms)	+2 to +3 points (MCI) +3 points (Mild AD)	-Clinician-administered and rated; answered by participant -Assessment of cognition -Validated
ADCS-ADL ADCS-iADL (subscale) ADCS-ADL-MCI (subscale)	0 to 78 (lower score = worse symptoms) 0 to 59 (lower scores indicative of more severe disease) 0 to 53 (lower scores = worse symptoms)	No data available	-Clinician—administered; completed by patient's caregiver -Assessment of function -Subscales not well validated
iADRS	0 to 144 (lower scores = worse symptoms)	-5 points (MCI) -9 points (Mild AD)	-Mathematical derivation based on scores obtained from the ADAS-Cog13 and ADCS-iADL -Integrated assessment of cognition and daily function -Not a preferred standalone assessment tool for primary efficacy per FDA
CDR-SB	0 to 18 (higher score = worse symptoms)	+1 point (MCI) +2 points (Mild and Moderate to Severe AD)	-Clinician administered/rated, semi-structured interview with patient and caregiver -Integrated assessment of cognition and daily function -FDA accepted as valid scale
MMSE	0 to 30 (lower score = worse symptoms)	-1 to -2 points (MCI) -2 points (Mild AD) (-1.4 to -3 points in Moderate to Severe AD)	-Clinician-administered/Answered by patient -Assessment of cognition -Validated

Abbreviations: AD = Alzheimer's disease; ADAS-Cog13 = 13-item cognitive subscale of the Alzheimer Disease Assessment Scale; ADCS-ADL = Alzheimer Disease Cooperative Study—Activities of Daily Living; ADCS-iADL = Alzheimer Disease Cooperative Study—Instrumental Activities of Daily Living; CDR-SB = sum of boxes of the Clinical Dementia Rating Scale; iADRS = Integrated Alzheimer Disease Rating Scale; MCI = mild cognitive impairment; MCID = minimum clinically important difference; MMSE = Mini-Mental State Examination.

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Canadian Agency for Drugs and Technologies in Health (CADTH), the Oregon Mental Health Clinical Advisory Group (MHCAG), and the Scottish Intercollegiate Guidelines Network (SIGN) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
Of the new systematic reviews identified since the last review, all were excluded due to poor quality (e.g., indirect network-meta-analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:
None identified.

New Formulations or Indications:
None identified.

New FDA Safety Alerts:

Table 3. Description of New FDA Safety Alerts[5]

Generic Name	Brand Name	Date of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
lecanemab	LEQEMBE	7/6/2023	Contraindications	Contraindicated in patients with serious hypersensitivity to lecanemab-irmb or to any of the excipients of LEQEMBI. Reactions have included angioedema and anaphylaxis.
			Boxed Warning	LEQEMBI, can cause amyloid related imaging abnormalities (ARIA) and serious and life-threatening events can occur. Serious intracerebral hemorrhage greater than 1 cm have occurred in patients treated with this class of medications. Testing for ApoE4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA.
			Warnings and Precautions	Hypersensitivity reactions, including angioedema, bronchospasm, and anaphylaxis, have occurred in patients who were treated with LEQEMBI. Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity reaction and initiate appropriate therapy. Infusion-related reactions confirmed at higher rates than placebo in second clinical trial

Randomized Controlled Trials:
No new RCTS were identified. A total of 227 citations were manually reviewed from the literature search. Only trials reporting new comparative evidence were considered for inclusion. After manual review RCTs were excluded due to wrong study design, comparator, outcome studied, or lack of reported comparative outcome data.

NEW DRUG EVALUATION:

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Donanemab is a monoclonal antibody that binds to beta-amyloid proteins in aggregated plaques found in patients with AD. Donanemab was approved by the FDA in 2024 for the treatment of Alzheimer's disease in populations with mild cognitive impairment or mild dementia. Approval was based primarily on results from a double-blind, phase 3 RCT comparing donanemab to placebo.

A phase 3, randomized, multicenter, double-blind, placebo-controlled trial (TRAILBLAZER-ALZ 2) evaluated the efficacy and safety of donanemab compared to placebo in patients with evidence of brain amyloid and a diagnosis of MCI or mild dementia due to AD.[1-3] The primary efficacy endpoint was the change from baseline to 76 weeks in cognition and function, as measured by the iADRS in both the overall combined population and in the subgroup of patients with low or medium levels of tau protein.[1-3] Secondary endpoints were change from baseline to 76 weeks in the CDR-SB, ADAS-Cog13, ADCS-iADL, MMSE, amyloid plaque reduction, tau PET (frontal cortical regions) change, and volumetric MRI (vMRI; whole brain, hippocampus, and ventricles) change in the low/medium tau or combined population.[1-3] Participants were required to have brain Aß pathology (> 37 Centiloids) and visual assessment of tau evidenced through PET scan. At Week 24 or Week 52, if the amyloid plaque level was <11 Centiloids on a single PET scan or 11 to <25 Centiloids on consecutive scans, the patient was to be switched to placebo in blinded fashion.[1,3] An MMSE score between 20 and 28 was required in addition to an informant- or self-reported gradual and progressive change in memory function for ≥6 months.[1,3] Efficacy analyses were performed for participants with a baseline and at least 1 postbaseline efficacy measurement based on randomized treatment.[1,3] A nonparametric rank analysis of covariance (ANCOVA) was performed of multiply imputed iADRS and CDR-SB at Week 76 for the intermediate tau and overall population.[1] To minimize functional unblinding of the rater to adverse events, all assessments after an ARIA-E event or infusion reaction were excluded.[1,3]

A total of 8240 subjects were screened for the study and 1736 individuals were selected and randomized 1:1 to receive 700 mg of donanemab intravenously (IV) 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 with stratification by site and tau pathology (low/medium or high).[1,3] Assessments were planned for every 4 weeks after randomization and after last dose.[1,3] At baseline there were 57% females and almost 90% were at least 65 years of age.[1,3] Sixteen percent of patients with AD were diagnosed with MCI and 84% had mild dementia. The mean MMSE score was 22.3 and the mean CDR-SB score was 3.9.[1,3] Roughly 70% of patients were ApoE4 carriers.[1,3] The other baseline characteristics of the study participants were generally similar between trial groups.[1,3] At week 76, the change from baseline in iADRS demonstrated a modest but statistically significant treatment effect in donanemab-treated patients compared to placebo in the low/medium tau population (MD 3.25 less decline [-35%], p<0.001) and also in the combined population (MD 2.92 less decline [-22%], p<0.001).[1-3] In relation to the 144-point scale range, a 3-point change compared to placebo represented a relatively small difference of about 2%. For secondary outcomes, there were modest but statistically significant changes that favored donanemab compared to

placebo in CDR-SB (combined: MD −0.67 [95% CI −0.92 to −0.43]; low/med tau: MD −0.68 [95% CI −0.94 to −0.42]; p<0.001 for both). Based on the 18-point scale, the changes compared to placebo represented about a 3.7% difference. Likewise, there were statistically significant changes that favored donanemab over placebo in the ADCS-iADL (combined: MD 1.70 [95% CI 0.84 to 2.57]; low/med tau: MD 1.83 [95% CI 0.91 to 2.75]; p<0.001 for both), in the ADAS-Cog13 (combined: MD −1.33 [95% CI −2.09 to −0.57]; low/med tau: MD −1.52 [95% CI −2.25 to −0.79]; p<0.001 for both), and in the MMSE (combined: MD 0.47 [95% CI 0.10 to 0.84], p=0.01; low/med tau: MD 0.48 [95% CI 0.09 to 0.87], p=0.02).[1,3] However, none of the secondary outcomes met the threshold levels for MCIDs reported in the literature.[4] The FDA reported in their analysis that when death was imputed as the worst score for the ADAS-Cog13, statistical significance was not achieved.[64] To address the potential effect of functional unblinding due to ARIA or infusion reactions, the investigators compared the results of the primary analysis to the results using a reduced dataset in which all assessments after occurrence of ARIA-E or infusion reaction were excluded and found the results were similar.[1] It was also reported that brain amyloid plaque levels decreased by 88.0 Centiloids (95% CI, −90.20 to −85.87) in donanemab treated patients compared to an increase of 0.2 Centiloids (95% CI, −1.91 to 2.26) in the placebo group for the low/medium tau population; in the combined population, amyloid plaque level decreased by 87.0 Centiloids (95% CI, −88.90 to −85.17) in donanemab treated patients and decreased by 0.67 Centiloids (95% CI, −2.45 to 1.11) in the placebo group.[1,3] At Week 76, the proportion of participants in the donanemab treatment arm who met dose stopping criteria based on amyloid PET results was 60%.[1] Approximately 12% of subjects randomized to donanemab had switched to placebo by weeks 28 through 52, and approximately 32% had switched to placebo by weeks 56-72.[1] The impact of amyloid beta reduction on clinical outcomes is uncertain as there has been no conclusive evidence to support a relationship between reductions in amyloid plaque levels and clinically meaningful symptom improvements in AD or a slowing of cognitive or functional decline.[65] There was no statistically significant change in Tau PET, but a greater decrease in whole brain volume, a lesser decrease in the hippocampal volume, and a greater increase in ventricular volume in the donanemab group than in the placebo group.[1,3] The cause and clinical relevance of these changes in brain volume is unclear.

The iADRS as a primary outcome measure has not been extensively validated in the medical literature. With the relatively small absolute effect size reported in the trial, it is unclear whether a roughly 3-point difference on the 144-point iADRS had clinically important effects in cognitive and functional outcomes (MCID = 5-points in MCI and 9-points in mild AD).[4,60] In addition, there were a higher number of discontinuations in the donanemab group compared to placebo which may have biased the outcome in favor of the intervention. In the study protocol, subjects who discontinued treatment would remain in the study to be evaluated for efficacy and safety assessments according to schedule.[1,3] However, the FDA highlighted that only 31/428 (7%) of subjects who discontinued treatment were followed up and completed the study.[64] It is unknown whether decreases in brain volume have an impact on disease progression or adverse effects. People identifying as White were over-represented in the trials and people identifying as Black were vastly under-represented, thereby limiting the applicability of the study results in more diverse real-world populations. It is unknown if donanemab has any benefit in moderate to advanced AD or if any reported benefit would be sustained if/when drug was to be discontinued. Longer, more robust trials are needed with donanemab treatment in order to provide definitive results in areas of clinical importance for individuals with early AD.[66,67]

Clinical Safety:

In the phase 3 (TRAILBLAZER-ALZ 2) trial, there was a higher percentage of deaths in the donanemab-treated patients compared to placebo (2.2% vs 1.2%, respectively).[1-3] There were 3 deaths associated with ARIA, one of which was caused by intracerebral hemorrhage.[1-3] There were more donanemab-treated patients who discontinued therapy compared to placebo (30% vs 20%, respectively).[1-3] Discontinuation due to an adverse event (AE) was reported in 13% of subjects compared to 4% on placebo.[1-3] Patients who discontinued treatment were often withdrawn by researchers from the study and excluded from the final analysis which lead to incomplete information on vital status.[1,64] Overall, there were 26% of donanemab-treated patients that withdrew from the study (8% due to an AE) compared to 20% on placebo (3% due to an AE).[1-3]

ARIA was reported in 36% of donanemab-treated patients versus 14% in the placebo group.[1-3] The incidence of ARIA was higher in ApoE4 homozygotes (donanemab: 55%; placebo: 22%) compared to heterozygotes (donanemab: 36%; placebo: 13%), but higher than placebo in both subgroups.[1-3] Symptomatic ARIA occurred in 6% of donanemab treated patients versus none on placebo.[1,2] The most common treatment emergent AEs associated with the use of donanemab compared to placebo, respectively, were ARIA-H microhemorrhages (25% vs 11%), ARIA-edema/effusion (24% vs 2%), ARIA-H superficial siderosis (15% vs 3%), headache (13% vs 10%) and infusion-related reactions (9% vs 0.5%).[1-3]

Table 4. Adverse Reactions Reported in at Least 5% of Patients Treated with Donanemab and at Least 2% Higher Than Placebo[1-3]

	Donanemab (N=853) N (%)	Placebo (N=874) N (%)
Total Subjects with any TEAE	758 (89)	715 (82)
ARIA-H microhemorrhages	217 (25)	100 (11)
ARIA- E (edema/effusion)	201 (24)	17 (2)
ARIA-H superficial siderosis	125 (15)	23 (3)
Headache	115 (13)	86 (10)
Infusion-related reactions	74 (9)	4 (0.5)
Abbreviations: ARIA-E = amyloid-related imaging abnormalities of edema/effusions; ARIA-H = amyloid-related imaging abnormality of microhemorrhages and hemosiderin deposits; TEAEs = treatment-emergent adverse events		

According to FDA labeling, the presence of amyloid beta pathology should be confirmed prior to therapy.[2] During treatment, if amyloid plaques are reduced to minimal levels on amyloid PET imaging, prescribers should consider stopping dosing with donanemab.[2] In the clinical trial, it was The FDA has issued a boxed warning for increased risk of ARIA (ARIA-E and ARIA-H) including symptomatic ARIA.[2] The warning also notes a higher incidence in ApoE4 homozygotes compared to heterozygotes and noncarriers.[3] Testing for ApoE4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA.[2] Prescribers are instructed to obtain a recent (within one year) brain MRI prior to initiating treatment with donanemab and ongoing MRIs prior to the 2nd, 3rd, 4th, and 7th infusions.[2] It is recommended that prescribers suspend dosing for patients with moderate to severe ARIA-E or ARIA-H observed on MRI or who are exhibiting clinical symptoms.[2] If the ARIA-E symptoms are mild (i.e. discomfort but no disruption of normal daily activity), prescribers may continue dosing based on clinical judgement.[2] Asymptomatic patients with mild ARIA-E or ARIA-H may continue supervised dosing, however, the safety data are limited and optimal timing and frequency of ARIA monitoring through MRI is unclear.[2] Donanemab FDA labeling contains a warning to also monitor for infusion related reactions including flu-like symptoms, nausea, vomiting, and changes in blood pressure.[2] If an infusion-related reaction should occur, prescribers may reduce the infusion rate or discontinue and treat as clinically indicated.[2] For discontinuations, a higher proportion of patients in the donanemab group discontinued therapy due to an adverse event compared to placebo (22% vs 12%, respectively).[1,3] The FDA determined that the conduct of trial further adds uncertainty to the observed mortality effect sizes and there is some evidence to suggest that additional vital status information from those that discontinued from the study may result in mortality effect sizes greater than those observed thereby suggesting increased levels of harm with donanemab relative to placebo.[64] Long-term clinical outcomes including mortality have not been studied with donanemab.[1,2]

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Cognitive Function
2) Quality of Life (e.g. physical/psychological autonomy)
3) Functional performance in activities of daily living (ADL)
4) Mortality
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Change in the iADRS score from baseline to 76 weeks

Table 5. Pharmacology and Pharmacokinetic Properties.[1-3]

Parameter	
Mechanism of Action	IgG1 monoclonal antibody directed against insoluble N-truncated pyroglutamate amyloid beta
Oral Bioavailability	N/A
Distribution and Protein Binding	Vd = 3.36 L; no information available on protein binding
Elimination	No information on route of elimination; Clearance = 0.0255 L/hr
Half-Life	12.1 days
Metabolism	Degraded by proteolytic enzymes

Abbreviations: IgG1 = Humanized immunoglobulin gamma 1; L = liter; N/A=not applicable; Vd = volume of distribution

Table 6. Comparative Evidence Table.[1,3]

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1.TRAILBLAZER-ALZ 2[1-3] NCT04437511	1. Donanemab (DON) 700 mg IV every 4 weeks 2. Placebo (PBO) IV every 4 weeks	Demographics: Mean age: 73 years Female: 57% Low/medium tau level: 68% High tau level: 32% ApoE4 (carriers): 70% Mean Baseline iADRS: 1. 105 2. 104 Mean MMSE: 22 CDR-SB: 3.9 Mean CDR global score: 0.5 = 60% 1 = 35% 2 = 3% Race, ethnicity White: 92% Asian: 6% Black or African American: 2% Key Inclusion Criteria: -Age 60 to 85 years - Progressive change in memory functions for ≥ 6mo (self-reported or observed) -Symptomatic AD -MMSE score 20 to 28 -Amyloid pathology (≥37 Centiloids) -Presence of tau pathology assessed by PET imaging Key Exclusion Criteria: Presence of amyloid-related imaging abnormalities of edema/effusion: > 4 cerebral microhemorrhages	ITT: 1. 860 2. 876 PP: 1. 853 2. 874 Attrition: 1. 255 (30%) 2. 176 (20%)	Primary Endpoint: iADRS CFB to Week 76, Low/medium-tau population: DON: −6.02 PBO: −9.27 MD (95% CI): 3.25 (1.88, 4.62); p<0.001 iADRS CFB to Week 76, Combined population: DON: −10.19 PBO: −13.11 MD (95% CI): 2.92 (1.51, 4.33); p<0.001 Secondary Endpoints: CDR-SB CFB to Week 76, Low/medium tau population: DON: 1.20 PBO: 1.88 MD (95% CI): −0.68 (−0.94, −0.42); p<0.001 CDR-SB CFB to Week 76, Combined population: DON: 1.72 PBO: 2.42 MD (95% CI): −0.67 (−0.92, −0.43); p<0.001 Change from baseline to 76 weeks in ADAS-Cog13, Low/medium tau population: MD −1.52 [95% CI −2.25 to −0.79]; p<0.001 Combined population: MD −1.33 [95% CI −2.09 to −0.57]; p<0.001	NA NA	Discontinuation due to adverse event: 1. 112 (13%) 2. 38 (4%) Deaths: 1. 17 (2.2%) 2. 10 (1.2%) SAE: 1. 140 (16%) 2. 124 (14%) TEAE 1. 758 (89%) 2. 715 (82%) Infusion reactions: 1. 74 (9%) 2. 4 (0.5%) Any ARIA 1. 314 (37%) 2. 130 (15%) ARIA-H (microhemorrhage) 1. 217 (25%) 2. 100 (11%) ARIA-E 1. 201 (24%) 2. 17 (2%) ARIA-H (superficial siderosis) 1. 125 (15%) 2. 23 (3%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Centralized, computer-generated randomization scheme using interactive web response systems. Baseline characteristics between groups were similar. Performance Bias: (High) High rates of infusion reaction and ARIAs in drug group versus placebo with blinding potentially broken during trial. Switch to placebo could complicate interpretation of adverse reactions overall in subjects originally assigned to donanemab. All assessments after an ARIA-E event or infusion reaction were excluded from analysis. Detection Bias: (Unclear) Clinical outcomes analyzed using complex NCS2 model that requires many assumptions. Measurements after death were treated as missing. A mixed model with repeated measures would be more typical and was used by FDA for their independent sensitivity analysis. Participants whose amyloid plaque reduction met dose reduction criteria had a double-blind dose reduction of donanemab to IV placebo for the remaining duration of the study. Attrition Bias: (High) High rates of discontinuations and missing data for both study groups. Protocol amendment with conflicting language that allowed participants to discontinue for events after treatment initiation without additional data collection. Patients with severe ARIA events were also excluded from analysis. Reporting Bias: (High) Sponsor did not make efforts to obtain vital status for subjects discontinuing from the trial which occurred at high rates in treatment group and may have affected mortality analysis. Outcomes reported as large cognitive improvements were relatively small and patients with severe ARIA events were excluded from analysis. Other Bias: (High) Funded by manufacturer; Most authors employed by manufacturer. Manufacturer responsible for design and conduct

		> 1 area of superficial siderosis -any intracerebral hemorrhage > 1 cm -severe white matter disease on MRI -Neurological disease that may affect cognition -Current serious or unstable illnesses including cardiovascular, hepatic, renal, gastrointestinal respiratory, endocrinologic, psychiatric, immunologic, or hematologic disease -History of clinically significant severe drug allergies		Change from baseline to 76 weeks in ADCS-iADL, Low/medium tau population: MD 1.83 [95% CI 0.91 to 2.75]; p<0.001 Combined population: MD 1.70 [95% CI 0.84 to 2.57]; p<0.001 Change from baseline to 76 weeks in MMSE, Low/medium tau population: MD 0.48 [95% CI 0.09 to 0.87], p=0.02 Combined population: MD 0.47 [95% CI 0.10 to 0.84], p=0.01		Headache 1. 115 (13%) 2. 86 (10%) Seizure 1. 3 (0.4%) 2. 1 (0.1%) P value and CI not reported		of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. **Applicability**: Patient: Of the 8240 subjects screened, 1736 were enrolled. The most common reasons for screening failure were low tau or amyloid pathology (50%) and MMSE score <20 or >28 (23%). Majority of patients identified as White (92%) limiting applicability to other populations. Intervention: Appropriate based on earlier phase 2 RCT testing. Comparator: Placebo appropriate for safety/efficacy; lecanemab available as future comparator. Outcomes: Mix of composite clinical scales and surrogate; Must establish surrogate amyloid lowering as clinically relevant; Longer term outcomes needed. Setting: United States, Poland, United Kingdom, Canada, Australia, Japan, Netherlands, Czech Republic.
Abbreviations: AD = Alzheimer's disease; ADAS-Cog13 = 13-item cognitive subscale of the Alzheimer Disease Assessment Scale; ADCS-ADL = Alzheimer Disease Cooperative Study—Activities of Daily Living; ADCS-iADL = Alzheimer Disease Cooperative Study—Instrumental Activities of Daily Living; AEs = adverse events; ApoE4 = apolipoprotein E; ARIA-E = amyloid-related imaging abnormalities of edema/effusions; ARIA-H = amyloid-related imaging abnormality of microhemorrhages and hemosiderin deposits; ARR = absolute risk reduction; CDR-SB = sum of boxes of the Clinical Dementia Rating Scale; CFB = change from baseline; CI = confidence interval; cm = centimeter; DON = donanemab; FDA = Food and Drug Administration; iADRS = Integrated Alzheimer Disease Rating Scale; ITT = intention to treat; IV = intravenous; MCI = mild cognitive impairment; MD= mean difference; mITT = modified intention to treat; MMSE = Mini-Mental State Examination; mo = months; MRI = magnetic resonance imaging; N = number of subjects; NA = not applicable; NCS2 = natural cubic splines with 2 degrees of freedom; NNH = number needed to harm; NNT = number needed to treat; PBO = placebo; PET =Positron Emission Tomography PP = per protocol; SAEs = serious adverse events; TEAEs = treatment-emergent adverse events								

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
donanemab-azbt	KISUNLA	VIAL	N
lecanemab-irmb	LEQEMBI	VIAL	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to September 26, 2024

1	lecanemab.mp.	335
2	donanemab.mp.	144
3	aducanumab.mp.	602
4	donepezil.mp. or Donepezil/	5319
5	galantamine.mp. or Galantamine/	2736
6	rivastigmine.mp. or Rivastigmine/	2364
7	memantine.mp. or Memantine/	4665
8	Alzheimer Disease/ or Alzheimer's.mp.	210608
9	1 or 2 or 3 or 4 or 5 or 6 or 7	12969
10	8 or 9	216514
11	limit 10 to (english language and full text and humans and (clinical trial, phase iii or clinical trial, phase iv or comparative study or guideline or practice guideline or randomized controlled trial or "systematic review") and last year)	227

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KISUNLA safely and effectively. See full prescribing information for KISUNLA.

KISUNLA (donanemab-azbt) injection, for intravenous use
Initial U.S. Approval: 2024

WARNING: AMYLOID RELATED IMAGING ABNORMALITIES
See full prescribing information for complete boxed warning.

Monoclonal antibodies directed against aggregated forms of beta amyloid, including KISUNLA, can cause amyloid related imaging abnormalities (ARIA), as ARIA with edema (ARIA-E) and ARIA with hemosiderin deposition (ARIA-H). ARIA is usually asymptomatic, although serious and life-threatening events can rarely occur. Serious intracerebral hemorrhages >1 cm have occurred in patients treated with this class of medications. ARIA-E can cause focal neurologic deficits that can mimic ischemic stroke. (5.1, 6.1)

ApoE ε4 Homozygotes

Patients treated with this class of medications, including 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. (5.1)

Consider the benefit for the treatment of Alzheimer's disease and risk of ARIA when deciding to treat with KISUNLA. (5.1, 14)

---------- INDICATIONS AND USAGE ----------

KISUNLA is an amyloid beta-directed antibody indicated 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)

----------DOSAGE AND ADMINISTRATION----------

- Confirm the presence of amyloid beta pathology prior to initiating treatment. (2.1)
- The recommended dosage of KISUNLA is 700 mg administered as an intravenous infusion over approximately 30 minutes every four weeks for the first three doses, followed by 1400 mg every four weeks. (2.2)
- Consider stopping dosing with KISUNLA based on reduction of amyloid plaques to minimal levels on amyloid PET imaging. (2.2)
- Obtain a recent baseline brain MRI prior to initiating treatment. (2.3, 5.1)
- Obtain an MRI 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. (2.3, 5.1)
- Dilution to a final concentration of 4 mg/mL to 10 mg/mL with 0.9% Sodium Chloride Injection, is required prior to administration. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 350 mg/20 mL (17.5 mg/mL) in a single-dose vial. (3)

---------- CONTRAINDICATIONS ----------

KISUNLA is contraindicated in patients with known serious hypersensitivity to donanemab-azbt or to any of the excipients. (4, 5.2)

----------WARNINGS AND PRECAUTIONS----------

- Amyloid Related Imaging Abnormalities (ARIA): Enhanced clinical vigilance for ARIA is recommended during the first 24 weeks of treatment with KISUNLA. Risk of ARIA, including symptomatic ARIA, was increased in apolipoprotein E ε4 (ApoE ε4) homozygotes compared to heterozygotes and noncarriers. The risk of ARIA-E and ARIA-H is increased in KISUNLA-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. (2.3, 5.1)
- 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. (5.3)

----------ADVERSE REACTIONS----------

Most common adverse reactions (at least 10% and higher incidence compared to placebo): ARIA-E, ARIA-H microhemorrhage, ARIA-H superficial siderosis, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 7/2024

Appendix 4: Key Inclusion Criteria

Population	Patients with Alzheimer's Dementia
Intervention	Drugs Listed in Appendix 1
Comparator	Drugs listed in Appendix 1 or placebo
Outcomes	Cognition, function, symptoms, disease progression, quality of life, morbidity, mortality
Timing	Any duration
Setting	Outpatient

Appendix 5: Prior Authorization Criteria

Alzheimer's Disease (Monoclonal Antibodies)

Goal(s):

- To support medically appropriate and safe use of Alzheimer Dementia drugs (as designated by the FDA)
- To limit off-label use of Alzheimer's Dementia drugs

Length of Authorization:

- Up to 6 months

Requires PA:

- Pharmacy point-of-sale and physician-administered claims

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Dosing and ARIA Monitoring

Drug	MRI Timing for ARIA Monitoring	Dosing	Frequency of Administration
Donanemab	Prior to Infusion 2 (no longer than 1 year)	See Prescribing Information for dosing recommendations	Every 4 Weeks
	Prior to Infusion 3		
	Prior to Infusion 4		
	Prior to Infusion 7		
	Annually		

Lecanemab	Prior to infusion 1 (no longer than 1 year) Prior to Infusion 5 Prior to Infusion 7 Prior to infusion 14 Annually	and for interruptions in therapy due to ARIA.	Every 2 Weeks
~~(Aducanumab)*~~	~~Prior to Infusion 1 (no longer than 1 year)~~ ~~Prior to Infusion 5~~ ~~Prior to Infusion 7~~ ~~Prior to Infusion 9~~ ~~Prior to Infusion 12~~ ~~Annually~~	~~----~~	~~Every 4 Weeks~~

*= Aducanumab no longer available after November 1, 2024.

ARIA = amyloid related imaging abnormalities; IV = intravenous; MRI = magnetic resonance imaging

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the drug to be used for treatment of a patient diagnosed with Alzheimer's Dementia **AND** has the prescriber ruled out other types of dementia (e.g., vascular dementia, Lewy body, and frontotemporal)?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request for continuation of therapy in a patient previously approved by FFS?	**Yes:** Go to Renewal Criteria	**No:** Go to #4
4. Is the therapy prescribed by or in consultation with a neurologist?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the patient between 50 and 90 years of age?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
6. Is there documented evidence that the patient has **mild** cognitive impairment due to Alzheimer's disease or **mild** Alzheimer's dementia as evidenced by the following assessments performed within the last 6 months: • Clinical Dementia Rating-Global Score (CDR-GS) of 0.5 or 1.0 **AND** • Mini-Mental Status Exam (MMSE) score between 22 and 30 (inclusive) **AND** • Positron Emission Tomography (PET) scan positive for elevated amyloid beta plaque or presence of elevated amyloid and/or elevated phosphorylated tau confirmed in cerebrospinal fluid (CSF)?	**Yes:** Go to #7 Document test results and dates. _____	**No:** Pass to RPh. Deny; medical appropriateness There is insufficient evidence for use of this agent in treating moderate or severe AD
7. Has the prescriber assessed and documented baseline disease severity within the last 6 months utilizing an objective measure/tool (e.g. Alzheimer's Disease Assessment Scale-Cognitive Subscale [ADAS-Cog], Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory-Mild Cognitive Impairment version [ADCS-ADL-MCI], Clinical Dementia Rating-Sum of Boxes [CDR-SB], MMSE, or other validated AD monitoring tool)?	**Yes:** Record baseline measurement. _____ Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Has the patient received a baseline brain magnetic resonance imaging (MRI) within 1 year prior to initiating treatment with no evidence of pre-treatment localized superficial siderosis or brain hemorrhage?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
9. Has the prescriber scheduled additional brain MRIs to be obtained as outlined in Table 1 to evaluate for the presence of asymptomatic amyloid related imaging abnormalities [**ARIA-E**]-edema (brain swelling) and/or [**ARIA-H**]-hemorrhage (brain bleeding or protein deposits on brain/spinal cord)?	**Yes:** Record scheduled appointment dates: _____ Go to #10	**No:** Pass to RPh. Deny; medical appropriateness
10. ~~Has~~ Is the patient ~~been screened to ensure they are not~~ currently receiving anticoagulant or antiplatelet therapy (excluding aspirin 81 mg)?	**Yes:** ~~Go to #11.~~ Pass to RPh. Deny; medical appropriateness	**No:** Go to #11. ~~Pass to RPh. Deny; medical appropriateness~~
11. Is there documentation based on medical records that the prescriber has tested the patient for the presence of apolipoprotein E4 (ApoE4) and, if a carrier, has discussed benefits and risks associated with therapy? Note: Patients who are ApoE4 homozygotes have a higher risk of ARIA, including symptomatic, serious, and severe radiographic ARIA compared to heterozygotes and non-carriers.	**Yes:** Approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there documented evidence that the patient has mild cognitive impairment due to Alzheimer's disease or mild Alzheimer's dementia as evidenced by the following assessments performed within the last 30 days: • Clinical Dementia Rating-Global Score (CDR-GS) of 0.5 or 1.0; **AND** • Objective evidence of cognitive impairment at screening; **AND** • Mini-Mental Status Exam (MMSE) score between 22 and 30 (inclusive)	**Yes:** Go to #2 Document test results and dates: _____	**No:** Pass to RPh. Deny; medical appropriateness
2. Is there documented evidence of follow-up MRIs performed and/or scheduled as recommended in Table 1 for therapy safety surveillance?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Was there a serious adverse event (symptomatic moderate to severe ARIA-H or ARIA-E [brain microhemorrhage, superficial siderosis, or edema]) observed or reported with therapy?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #4
4. Has the patient received at least 6 months of uninterrupted therapy?	**Yes:** Go to #5	**No:** Approve remaining duration of the 6-month titration period
5. Is the request for donanemab?	**Yes:** Go to #6	**No:** Go to #8
6. Has PET imaging been performed within the last 6 months to confirm the presence of amyloid plaques?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
7. Does the patient have amyloid plaque levels at <11 centiloids on a single PET scan or 11 to <25 on consecutive months	**Yes:** Pass to RPh. Deny; medical Appropriateness In clinical studies, dosing was stopped based on a reduction of amyloid levels below predefined thresholds on PET imaging.	**No:** Go to #8
8. Is there documentation that, compared to baseline assessment, therapy has resulted in: • cognitive or functional improvement **OR** • disease stabilization **OR** • a reduction in rate of clinical decline compared to the natural disease progression? The same clinical measure used to assess AD (e.g., CDR-GS, MMSE, ADAS-Cog, ADCS-ADL-MCI, etc) is recommended to document clinical benefit.	**Yes:** Approve for up to 6 months Document benefit: _____	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 12/24(DE);10/23;10/21
Implementation: TBD