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Drug Class Update with New Drug Evaluation: Alzheimer's Disease Drugs

Date of Review: October 2023

Date of Last Review: October 2021
Dates of Literature Search: 07/01/2021 – 06/22/2023
Brand Name (Manufacturer): Leqembi (Eisai Inc)
Dossier Received: yes

Generic Name: lecanemab-irmb

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, lecanemab, in the treatment of Alzheimer's dementia (AD). This review will also evaluate the 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, but there are some medicines called acetylcholinesterase inhibitors (ACHEIs) that work to increase levels of chemical messengers in the brain. These medicines may help people with AD think or speak more clearly or make them able to take better care of themselves. However, these medicines may only have a small benefit and usually work for a short amount of time (6 to 9 months). Also, these medicines may cause upset stomach, weight loss, or stomach pain/cramping.
- A review found that stopping ACHEIs (donepezil, galantamine, rivastigmine) within 2 months after starting treatment may make a person not able to think as well. The effects of stopping these ACHEI medicines 3-11 months after starting is unclear. There is some good evidence that at 12 months or after, stopping an ACHEI medicine may make a person less able to be active or take care of themselves than if they kept taking it.
- A different review looked at ACHEIs in people not able to think clearly because of low blood flow to the brain. The review found that donepezil 10 mg daily and galantamine 16 mg to 24 mg daily helped improve thinking ability. There was also good evidence that donepezil 10 mg daily may slightly improve a person's ability to care for themselves, but the individual is unlikely to notice the change.
- A new medicine, lecanemab (LEQEMBE), is used to treat patients with mild AD to help clear the brain of harmful proteins that might worsen AD. However, patients taking lecanemab may have a high risk of developing brain swelling or brain bleeding side-effects when using this drug, so treatment must be closely watched. At this time, there is not good evidence that these types of medicines help a patient think more clearly, remember or help them do daily tasks.

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- The Drug Use Research and Management group recommends that lecanemab 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 lecanemab compared to placebo or currently available treatments for Alzheimer's disease (AD)?
2. What is the safety of lecanemab compared to placebo or currently available treatments for AD?
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:

- This update includes information from two high-quality systematic reviews[1,2] and two randomized control trials (RCTs).[3,4] There is low quality evidence from a systematic review that, compared to continuation of AChEIs, discontinuation of AChEI treatment may be associated with worse cognitive function based on standardized scales [which include the Alzheimer's Disease Assessment Scale-Cognitive subscale/11 (ADAS-Cog/11) and Mini-Mental State Examination (MMSE)/Standardized MMSE (SMMSE)] at up to 2 months (standardized mean difference (SMD) -0.42, 95% confidence interval (CI) -0.64 to -0.21), but the effect over 3-11 months is very uncertain (SMD -0.40, 95% CI -0.87 to 0.07; 3 RCTs; very low quality evidence).[1]
- Discontinuation of an AChEI (compared to continuing treatment) likely resulted in:
    - greater functional impairment at 12 months (MD -3.38 Bristol Activities of Daily Living Scale (BADLS) points, 95% CI -6.67 to -0.10) based on moderate quality evidence.[1]
    - little to no change in neuropsychiatric status at 12 months (MD -0.87 Neuropsychiatric Inventory (NPI) points; 95% CI -8.42 to 6.68) based on low quality evidence.[1]
    - worse cognitive function at 12 months (MD -2.09 Standardized Mini-Mental State Examination (SMMSE) points, 95% CI -3.43 to -0.75) based on moderate quality evidence.[1]
- There was high-quality evidence that at 24 weeks donepezil 10 mg daily and galantamine 16 mg to 24 mg daily at 26 weeks resulted in a modest beneficial effect on cognition compared to placebo in people with vascular cognitive impairment (VCI) as measured by the ADAS-Cog 11 tool (donepezil: MD -2.18 [95% CI −3.87 to −0.47]; galantamine: MD -1.84 [95% CI −3.63 to −0.14]).[2] There was moderate-quality evidence from 2 RCTs that donepezil 10 mg daily may slightly improve functional performance based on the Alzheimer's Disease Functional Assessment and Change Scale (ADFACS), although the size of the change is unlikely to be clinically important (MD −0.95 [95% CI −1.73 to −0.17]).[2] Galantamine 16 mg to 24 mg, donepezil 10 mg, and rivastigmine may be associated with slightly more adverse events compared to placebo based on low-quality evidence.[2]
- The Food and Drug Administration (FDA) recently approved donepezil once-weekly transdermal patch formulation.[8]
- The FDA issued a safety alert for worsening symptoms of extrapyramidal disorders with galantamine and amyloid-related imaging abnormalities with aducanuamb-avwa.[9,10]
- Lecanemab is an anti-amyloid beta (Aß) monoclonal antibody that received approval in January 2023 for the treatment of early AD.[6] One phase 2b, dose-finding trial (Study 201) and one phase 3 RCT (Study 301) compared lecanemab to placebo and were evaluated for FDA approval.[3-7]
    - In Study 201 lecanemab 10 mg/kg biweekly dosing regimen was unable to meet its prespecified primary endpoint as it failed to show a significant difference from placebo in the Alzheimer's Disease Composite Score (ADCOMS) cognitive function assessment. The ADCOMS contains 12 items that include components of the ADAS-Cog, MMSE, and Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) cognitive and functional ability total scores.

- In Study 301, the CDR-SB score from baseline favored lecanemab compared to placebo (mean difference [MD] 0.45; 95% CI, -0.67 to -0.23; P<0.001; insufficient evidence) at 18 months.[7] There were statistically significant changes in the secondary outcome measures of ADAS-Cog14 score (MD -1.44; 95% CI, -2.27 to -0.61; insufficient evidence), the ADCOMS (MD -0.05; 95% CI, -0.074 to -0.027; insufficient evidence), the ADCS-MCI-ADL (MD 2.0; 95% CI, 1.2 – 2.8; insufficient evidence) for lecanemab-treated groups compared to placebo (P<.001 for all). A substudy of amyloid burden on Positron Emission Tomography (PET) reported that brain amyloid burden showed a statistically significant dose- and time- dependent amyloid reduction with lecanemab therapy compared to placebo at 18 months (adjusted mean difference -59.12 [95% CI, -62.64 to -55.60; p<0.001]; insufficient evidence).[7] There is insufficient evidence to assess the clinical significance of these endpoints and whether changes in amyloid levels has an effect on cognitive decline.
- The most common adverse events associated with lecanemab were infusion reactions, ARIA-H ("hemorrhage" including combined cerebral microhemorrhages, cerebral macrohemorrhages, and superficial siderosis), ARIA-E (edema/effusion), headache and falls.[4-7] Long-term clinical outcomes including mortality have not been studied with lecanemab.
- Evidence for lecanemab comes from trials enrolling predominately people who identify as White, with mild AD, and between 50-90 years of age.[2,3] There is insufficient evidence on efficacy or harms data for people who identify as Black (only 2% of enrolled participants) and other important factors such as ethnicity and socioeconomic status or with health concerns such as people with a risk of bleeding, [2,3]

- 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.[7,10]

Recommendations:

- Create a new PDL class: Monoclonal Antibodies for Alzheimer's Disease.
- Designate lecanemab as non-preferred on the preferred-drug list (PDL).
- Implement prior authorization (PA) criteria for lecanemab and update existing criteria as proposed (**Appendix 5**).

Summary of Prior Reviews and Current Policy

- Therapies FDA-approved for the treatment of AD were previously reviewed by the Pharmacy and Therapeutics (P&T) Committee in October 2021.
- Previous evaluations concluded that there was insufficient evidence for the treatment of AD beyond 6 months.
- 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.
- 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 are numerous AChHEIs and memantine formulations available on the preferred drug list (PDL) that do not require PA (**See Appendix 1**)
- There is insufficient evidence that use of aducanumab in patients with AD has any 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 2021.
- Aducanumab treatment resulted in an increased incidence of amyloid-related imaging abnormalities (ARIA) including brain microhemorrhage and edema compared to placebo.

- There was insufficient evidence to verify long-term safety of aducanumab, which is especially a concern in patients with pre-existing risk factors for bleeding, including concomitant medications that could increase the risk for bleeding.
- No comparative efficacy or safety data were available for aducanumab versus other agents used to treat AD.

Background:
Alzheimer's disease (AD) is a progressive condition of neurological degeneration and memory impairment that primarily affects the elderly.[11] Alzheimer's dementia is a complex disorder that may be the result of numerous factors such as genetics, environmental stimuli, age, and education.[11] Generally, AD is characterized by deterioration of cognitive and reasoning skills, poor coordination and muscle function, personality changes, and an incapability of autonomous self-care.[11] Common neurological manifestations of AD include episodic memory impairment, a decline in visual-spatial perception, a reduced capability to learn, problem-solve, and complete mathematical calculations, a decreased ability to think in abstract, and overt lapses in judgement.[11] Alzheimer's dementia is the most common form of dementia and accounts for 60-80% of all dementia cases.[11] The prevalence of AD appears to increase dramatically with age.[11,12] 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.[11,12] By 85 years of age and older, around one-third of the population is estimated to have some form of AD.[11,12] Currently in the United States, an estimated 6 million people aged 65 or older have AD and it is projected that by 2060 the number may surge to almost 14 million.[12] Studies are inconclusive whether the incidence of AD differs among men and women, but there is some evidence to suggest a disproportionately higher incidence among Black, African and African American persons than other racial or ethnic groups.[11]

The diagnosis of AD may be challenging and often requires a review of clinical findings, medical history, and brain imaging.[11-13] Evaluation involves ascertainment of medical history from the patient and family member (or caregiver) along with a cognitive and neurologic examination.[12-14] The clinical spectrum of AD may range from asymptomatic to severe impairment.[11-14] Early disease without symptoms may be characterized as preclinical AD.[11-14] As neuronal injury and amyloid develops, there may be subtle decline in memory, organization, and mood where the patient would be diagnosed with mild cognitive impairment (MCI).[12] Medications that could cause cognitive impairment should be discontinued where possible and behavioral symptoms treated.[15] The American Academy of Neurology also recommends that clinicians assess for MCI with validated tools and monitor the cognitive status of their patients with MCI over time.[15] 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).[16,17] When changes in personality, speech, and cognition occur that result in functional impairment, a clinical diagnosis of AD is often made.[16,17] AD may be classified as mild, moderate, or severe depending upon the extent that cognitive decline interferes with ADLs.[13] Early-onset AD (EOAD) is rare and generally manifests before 65 years of age.[12] Mutations in the genes for amyloid precursor protein, presenilin 1, or presenilin 2 usually cause EOAD.[12,18] Late-onset AD (LOAD) affects most (greater than 95%) people with AD and typically occurs after 65 years of age.[12] 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.[33,34]

There have been several factors identified that increase the risk of AD development.[12,18] Advanced age, family history/genetics, Down syndrome, previous head trauma, and environmental pollutants may predispose individuals to AD.[12,18] 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.[12,19] 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.[19,20] Modifiable risk factors for AD may include low education level, diabetes mellitus, hypertension, and a sedentary lifestyle.[16,17] Alzheimer's dementia generally has a slow onset and progresses gradually over many months or years.[13]

Although the precise cause of AD is not well understood, there are common neuropathogenic aspects such as amyloid-beta (Aβ) and tau protein that have been the focus of most modern research.[20,21] Physiologic amounts of Aβ peptide enhance memory, and tau protein appears to have an important role in neuronal

microtubule assembly .[20,21,23] However, an imbalance of these key proteins by overproduction or dysregulation may lead to accumulation of plaques and neurofibrillary tangles.[21-23] Aβ plaques exist in many different conformational states (monomers, oligomers, protofibrils, and insoluble fibrils) and some forms may be more neurotoxic than others.[21] Studies of the Arctic Alzheimer Mutation (AβPP E693G) have reported observance of high levels of soluble Aβ protofibrils in people with AD.[20-22] High levels of amyloid-beta increases glycogen synthase kinase 3B and phosphorylates tau.[20,23] It has been hypothesized that as amyloid beta aggregates and triggers tau phosphorylation, it leads to neurofibrillary tangle (NFT) formation, followed by synapse degradation and disruption of neuron signaling, and eventual neuronal destruction and death.[20,24] Whether tau tangle pathology precedes AB plaque formation is still under investigation.[20-22] Nevertheless, a direct correlation between mean plaque count and cognitive performance is controversial as at least one study has shown that in about one-quarter of elderly deaths with significant plaque accumulation, the individuals were not cognitively impaired.[20] Regardless of the root cause, neuronal damage results in widespread neurotransmitter deficiencies including those involved in the cholinergic pathway.[25-27] 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.[25-27]

A variety of brain imaging techniques are available to help confirm the presence of AD.[28-31] Classic magnetic resonance imaging (MRI) is useful in detection of low oxygen levels and reduced brain blood flow commonly observed in patients with AD.[30,31] Aβ plaques and NFTs are easily visible with Positron Emission Tomography (PET) neuroimaging.[29-31] 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.[29,30] The standardized uptake value ratio (SUVR) is a method to quantify the degree of radioactive tracer uptake in the subject's brain. For imaging with amyloid and tau, SUVR is commonly calculated using the unaffected cerebellum as a reference.[49] Accumulation of tau may also be measured in the cerebral spinal fluid (CSF) and can serve as a biomarker of neuronal degeneration.[20,32] Detection of low levels of Aβ 42 or elevated hyperphosphorylated tau in the CSF are trademarks of AD.[28] 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).[5,32]

Since there is no known cure for AD, treatment involves symptom management and strategies to reduce long-term clinical decline.[12] A multifactorial approach will generally involve nonpharmacologic and behavioral interventions as well as pharmacotherapy.[12] Current FDA-approved therapies for AD include ACHEIs, the N-methyl-D-aspartate (NMDA) antagonist memantine, and the human monoclonal antibodies.[13,23,35] ACHEIs function to increase acetylcholine in the central nervous system via suppression of the metabolizing enzyme acetylcholinesterase.[13] ACHEIs (e.g. donepezil, galantamine, rivastigmine) are typically used as first-line therapy in mild to moderate dementia to alleviate AD symptoms.[13,15] Memantine blocks the excitatory effects of glutamate by the preferential binding to NMDA receptor channels to facilitate synaptic transmission, neuronal growth and differentiation.[13] 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.[13.20] The newer monoclonal antibodies are approved for mild AD and target the aggregated forms of amyloid beta plaques which includes soluble oligomers and insoluble fibrils.[36] Widespread use of monoclonal antibodies in patients with AD has been limited likely due to unknown clinical advantages and high cost. Overall, ACHEIs, NMDA antagonists, and monoclonal antibodies have reported only modest treatment effects in different stages of AD.[13] 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 [6,13,37]

Generic Name	Brand Name	Typical Dose/Route/Frequency	FDA Approved AD Indication	Advantages	Safety Concerns
Donepezil	Aricept™, Aricept ODT™	5 mg or 10 mg orally once daily	Mild to Moderate	Prescriber familiarity; generic, orally	Nausea, vomiting, loss of appetite, increased frequency of bowel

		10 mg or 23 mg orally once daily	Moderate to Severe	disintegrating tablet available	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
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	
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	
Memantine + Donepezil	Namzaric™	If stabilized on donepezil 10 mg and NOT on memantine: Memantine ER 7 mg/donepezil 10 mg once daily in the evening up to target memantine ER 28 mg/ donepezil 10 mg once daily	Moderate to Severe	Combination for reduced pill burden	All of the above
Aducanumab	Aduhelm™	10 mg/kg once every 4 weeks	Mild	Unknown	ARIA including brain edema and microhemorrhage; cerebral hemorrhage; seizures
Lecanemab	Leqembe™	10 mg/kg 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.[23] Several MABs have been developed to either decrease amyloid beta production, hinder beta-amyloid aggregation, or increase amyloid beta clearance, but none of these agents have been able to demonstrate a definitive clinical benefit associated with changes in amyloid beta levels.[23] These agents differ in selectivity for Aβ polymorphic variants and their epitopes.[38] However, studies with amyloid modifying therapies and specifically amyloid-beta targeting MABs (e.g. bapineuzumab, aducanumab, lecanemab) have revealed their own unique safety risks collectively known as ARIA.[39,40] ARIA may be observed in patients who have undergone a MAB infusion as a result of anti-Aβ autoantibody development in the CSF.[39,40] MRI with ARIA findings may reveal brain swelling or microhemorrhages referred to as ARIA-edema (ARIA-E) and ARIA-hemorrhage (ARIA-H), respectively.[39,41] ARIA may present with headache, confusion, visual changes and gait difficulty usually observed between the first and third therapy infusion.[41] Serious ARIA symptoms may include seizures, encephalopathy, stupor, and focal neurologic deficits. 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.[35] 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.[19,40] In studies of patients treated with aducanumab and lecanemab, 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.[40] 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.[7,10]

Clinically important outcomes in AD include mortality, cognitive function, quality of life/independence, functional performance in activities of daily living (ADL), behavioral disturbances, and serious adverse events.[43] 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 minimal clinically important differences (MCIDs) in many AD therapy outcomes.[17] The SMMSE and MMSE are similarly designed and commonly used scales to assess cognitive impairment in AD (30 points possible, higher is better, 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).[44,45] Both scales have 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).[44-46] Factors such as education level may influence SMMSE/MMSE scoring.[44-46] Although some studies have reported the minimum clinically important difference thresholds for the SMMSE/MMSE to be 1.4 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).[45] In mild AD, studies have used the Clinical Dementia Rating Scale (CDR) which include the CDR-Sum of Boxes (CDR-SB) and Global CDR Score (CDR-GS) that measure cognitive and functional impairment in AD.[48] The CDR 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.[48] A qualified rater uses the interview data and clinical judgment to assign scores for each domain.[48] The CDR-GS ranges from 0 to 3 and dementia rating may be scored as none (0), questionable cognitive impairment/very mild dementia (0.5), mild cognitive impairment/mild dementia (1), moderate dementia (2), and severe dementia (3).[48] The CDR-SB score has a range from 0 (normal) to 18 (severe dementia).[42] A CDR-SB score of 0 is considered normal while the higher scores may be characterized in the following manner: 0.5-4.0 = questionable cognitive impairment to very mild dementia; 4.5-9.0 = mild dementia; 9.5-15.5 = moderate dementia; 16.0-18.0 = severe demetia.[42] 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.[42,48] An increase of 1- to 2-points on the CDR-SB was found to be clinically significant by the National Alzheimer's Coordinating Centers (NACC) Uniform Data Set (UDS).[42] Other validated instruments for AD outcome assessment include the Functional Activities Questionnaire (FAQ; 30 points possible, lower score is better; MCID defined as 3 to 5 points), the Alzheimer's Disease Assessment Scale-Cognition (ADAS-Cog) for cognitive assessment in mild to severe AD (11 subject-completed tests and observer assessments of memory, language, and critical thinking; ADAS-Cog14 includes all 11 items plus a test of word recall, number cancellation, and a maze with a score ranging from 0-90 with higher scores reflecting greater impairment; MCID = 2 points for MCI due to AD and ≥3 points for mild AD, lower score better), the 24-item Alzheimer's Disease Cooperative Study—Activities of Daily Living (ADCS-ADL) instrument (range from 0 to 78; higher score is better; MCID not defined) or 18-item ADCS-ACL Mild Cognitive Impairment (MCI) instrument (range from 0 to 57; higher score better; MCID not defined), and the 40-question severe impairment battery (SIB; 100 points possible, lower score=worse; MCID not defined).[28,50-53] The Bristol Activities of Daily Living scale (BADLS) is a tool used in AD patients for assessment of functional ability. The BADLS was developed for self-completion by caregivers of patients with dementia to assess basic activities of daily living (ADL) and instrumental ADLs. The BADLS has 20 questions rated on a 4-point scale with possible scores from 0 points (no help required) to 3 points (unable even with supervision) with a range 0 – 60 points (MCID = 3.5 points).[62] Quality of life in patients with AD may be measured with the Alzheimer's Disease Functional Assessment and Change Scale (ADFACS; 16 items, range 0 to 54, higher scores = more severe impairment).[54] A two-point difference on the ADFACS between cognitively normal people and those with mild cognitive impairment in Alzheimer's disease may be clinically significant according to some research.[54] The ADCOMS is a manufacturer-developed 12-item weighted combination of items from 3 commonly used clinical scales: 4 items from the ADAS-Cog (delayed word recall, orientation, word recognition, and word finding), two items from the MMSE (orientation to time and drawing), and 6 items from the CDR-SB (personal care, home and hobbies, community affairs, judgment and

problem solving, orientation, and memory).[55] More studies are needed to evaluate whether the ADCOMS may be recognized as a valid clinical tool for assessment of MCI due to AD and dementia.[55,56]

Although the FDA typically performs a risk-benefit assessment in their reviews, MCID thresholds have not always been required prior to approval.[43] In recent years, the FDA has granted accelerated approval for many drugs based on evidence from unpublished studies with smaller patient populations, limited follow-up, and intermediate biomarkers that currently do not have established clinical significance.[57] For example, the human monoclonal antibody aducanumab was studied in 2 phase 3 placebo-controlled RCTs (study 302 "EMERGE" and study 301 "ENGAGE") that included patients with MCI or mild dementia due to AD who had evidence of amyloid plaques verified via PET scan.[48,58] Study 302 demonstrated a modest but statistically significant benefit compared to placebo at week 78 for the primary outcome of CDR-SB (absolute difference -0.39 points; P=0.01), while study 301 failed to show benefit.[48,58] Neither trial was able to establish a clinically meaningful difference from placebo; however, aducanumab was shown to remove amyloid beta in both trials in a dose-dependent manner.[48,58] Adverse effects such as ARIA were reported in over 40% of trial participants who received the higher dose of aducanumab and 25% of these cases were symptomatic (e.g. confusion, dizziness, headaches).[48,58] Using brain AB plaque reduction as a biomarker, the FDA approved aducanumab based on the conclusion that this surrogate endpoint might predict a future clinical benefit.[48,58] However, regulatory reviews by Health Canada and the European Medicines Agency (EMA) found the trial data insufficient to support marketing approval and therefore aducanumab is not currently approved for use in Canada or Europe.[58]

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, and the Canadian Agency for Drugs and Technologies in Health (CADTH) 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:

Cochrane - Withdrawal or continuation of ACHEI or memantine or both, in people with dementia.[1]

A 2021 Cochrane review evaluated the effects of withdrawal or continuation of ACHEIs or memantine, or both, in people with dementia. Participants were adults (n=759) with dementia due to AD that ranged in severity from mild to very severe and who were being actively treated with ACHEIs.[1] Seven RCTs of 6 weeks to 12 months duration were included. Results were categorized into three outcome assessment time periods: short-term (≤2 months), medium-term (3 to 11 months), and long-term (12 months or more).[1] Six of the trials investigated the effects of stopping an ACHEI while one trial examined the discontinuation of either donepezil or memantine. The mean age range of participants was 72.7 to 89.2 years.[1] The primary endpoints were change from baseline in cognitive function (based on ADAS-Cog/11 and MMSE), neuropsychiatric and functional outcomes (NPI, BADLS, ADCS-ADL), rates of institutionalization, adverse events, dropout from trials, mortality, quality of life and care-related outcomes.[1]

Four studies found low quality evidence that discontinuation of ACHEI treatment may be associated with worse cognitive function within 2 months compared to continuation (standardized mean difference (SMD) -0.42, 95% CI -0.64 to -0.21), but the effect of discontinuation versus continuation over medium time periods

(within 3 to 11 months) is very uncertain.[1] One study with moderate quality evidence found that discontinuation of ACHEI likely results in reduced cognitive function at 12 months (MD -2.09 SMMSE points, 95% CI -3.43 to-0.75).[1] There was one study with moderate quality evidence that reported discontinuation of an ACHEI likely resulted in greater functional impairment than continuing treatment at 12 months or longer (MD -3.38 Bristol Activities of Daily Living Scale (BADLS) points, 95% CI -6.67 to -0.10).[1] Discontinuation was shown to possibly worsen of neuropsychiatric symptoms over the short term and medium time periods, but all evidence was considered to be of very low quality.[1] Moderate quality evidence from one study suggest that discontinuing an ACHEI is probably associated with worse cognitive function after long-term treatment (MD -2.09 Standardized Mini-Mental State Examination (SMMSE) points, 95% CI -3.43 to -0.75).[1] There was no clear evidence found to show that discontinuation had an effect on dropout from trials, deterioration in overall medical condition, adverse events, institutionalization, or mortality.[1] The authors were unable to determine whether the effects of ACHEI discontinuation differed according to dementia severity at baseline.[1]

Cochrane- ACHEIs for vascular dementia and other vascular cognitive impairments: a network meta-analysis[2]

A 2021 systematic review and network meta-analysis evaluated the role of treating vascular dementia and other vascular cognitive impairments (VCI) with ACHEIs.[2] Eight RCTs (n=4373) were included with durations from 24 to 26 weeks.[2] Studies included RCTs in which donepezil, galantamine, or rivastigmine were compared with placebo in participants who had vascular dementia or other VCI (excluding cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)).[2] Mean ages of participants were between 72.2 and 73.9 years. Only oral formulations were assessed.[2] The primary outcomes of interest were cognitive function (ADAS-Cog), clinical global impression, functional performance in ADL, and number of adverse events.[2] All included trials were manufacturer-sponsored with low to unclear risk of bias and evidence grading ranged from very low to high-quality.[2]

There was high-quality evidence for donepezil 10 mg daily at 24 weeks and galantamine 16 mg to 24 mg daily at 26 weeks which suggests a modest beneficial effect on cognition compared to placebo in people with VCI as measured by the ADAS-Cog tool (donepezil 10 mg: MD -2.18 [95% CI −3.87 to −0.47]; galantamine 16 to 24 mg: MD -1.84 [95% CI −3.63 to −0.14]).[2] There was moderate-quality evidence that donepezil 10 mg daily may slightly improve functional performance based on the ADFACS, although the size of the change is unlikely to be clinically important (2 trials, 813 participants: MD −0.95 [95% CI −1.73 to −0.17]; used last observation carried forward (LOCF).[2] Studies with rivastigmine showed no significant difference from placebo in cognition or functional performance in ADL based on low quality evidence. All Galantamine 16 mg to 24 mg daily, donepezil 10 mg daily, and rivastigmine may be associated with slightly more adverse events compared to placebo based on low-quality evidence.[2] There was no evidence of increased numbers of serious adverse events or deaths with any of the ACHEIs included in the review.[2]

After review, 5 systematic reviews 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:

A new once-weekly transdermal patch formulation of the ACHEI donepezil (ADLARITY) was approved in March 2022 for the treatment of mild, moderate, and severe dementia of the Alzheimer's type.[8] Donepezil received initial US approval in 1996 and is currently available generically in 5 mg, 10 mg, and 23 mg oral tablets as well as 5 mg and 10 mg oral disintegrating tablets.[8] ADLARITY was approved through FDA's 505(b)(2) regulatory pathway which enabled results from

previous studies with donepezil tablets to be compared with the transdermal patch formulation.[8] Pharmacokinetic data assessed over a 5-week period in 60 healthy volunteers demonstrated that the 5 mg/day or 10 mg/day weekly patch had similar bioavailability as the oral tablets.[8]

The most common adverse reactions occurring in healthy subjects receiving donepezil transdermal system 10 mg/day were headache (15%), application site pruritus (9%), muscle spasms (9%), insomnia (7%), abdominal pain (6%), application site dermatitis (6%), constipation (6%), diarrhea (4%), application site pain (4%), dizziness (4%), abnormal dreams (4%), and skin laceration (4%).[8] Following the removal of donepezil transdermal systems, some participants experienced skin irritation, including erythema (64.6%), papules (16.0%), and edema (0.4%), but none of the transdermal systems were discontinued because of skin irritation.[8] ADLARITY is contraindicated in those with hypersensitivity to donepezil or to piperidine derivatives or patients with a history of contact dermatitis with its use.[8]

New FDA Safety Alerts:

Table 2. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, Contraindications)	Addition or Change and Mitigation Principles
Galantamine[9]	Razadyne; Razadyne ER	8/2021	Warning	An increase in cholinergic tone may worsen symptoms related to extrapyramidal disorders
Aducanumab-avwa[10]	Aduhelm	2/2023	Warning	Extensive changes to the warnings and precautions regarding ARIA-E and ARIA-H. See full prescribing information for details. *"ARIA is usually asymptomatic, although serious and life-threatening events, including seizure and status epilepticus, rarely can occur. Rarely, fatal events have occurred in the setting of ARIA… When present, reported symptoms associated with ARIA may include headache, confusion, visual changes, dizziness, nausea, and gait difficulty. Focal neurologic deficits may also occur…. Consider testing for ApoE ε4 carrier status to inform the risk of developing ARIA when deciding to initiate treatment with ADUHELM."* *… although ARIA can occur in any patient treated with ADUHELM, there is an increased risk in patients who are ApoE-E4 homozygotes"*
Abbreviations: ApoE-E4= ARIA-E= amyloid-related imaging abnormalities-edema; ARIA-H=amyloid related imaging abnormalities-hemorrhage				

Randomized Controlled Trials:
A total of 144 citations were manually reviewed and excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

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:
Lecanemab (LEQEMBE) is the latest anti-amyloid beta (Aß) monoclonal antibody that received FDA approval in January 2023 for the treatment of early AD.[4] The safety and efficacy of lecanemab in patients with MCI due to AD or mild dementia due to AD was evaluated in 2 industry-sponsored studies.[4-6] Both studies were randomized, double blind, placebo controlled, parallel group, multicenter trials.[4-6] Study 201 was a phase 2b dose-finding trial (N=856) and study 301 was a phase 3 confirmatory study (N=1795). More details on study design and risk of bias are included in **Table 5**.

Study 201
The primary outcome in study 201 was the change from baseline in the Alzheimer's Disease Composite Score (ADCOMS) at 12 months (week 53).[3-6] Key secondary efficacy endpoints included the change from baseline in amyloid PET SUVR composite at Week 79 and change from baseline in the CDR-SB and ADAS-Cog14 at Week 79.[3-6] The population included an equal amount of male and female patients age 50 to 90 years (mean 71.3 years) all with evidence of Aβ pathology via PET scan or CSF assessment.[3-6] At baseline, the patients had a mean CDRSB score of 2.9, and 60% of patients had a MMSE score between 22 and 26 (mild dementia) while 40% had an MMSE score between 27 and 30 (questionable to no dementia).[3-6] Participants included 71% ApoE e4 carriers and 29% were ApoE e4 non-carriers.[3-6] Over half (54%) of the patients were on concomitant ACHEIs and/or memantine at the start of the study.[3-6] Patients were excluded if they had any other memory impairment besides AD associated with cognitive impairment, history of cardiovascular disease (TIA, stroke), seizures, an uncontrolled bleed, uncontrolled diabetes, hypertension, evidence of brain microhemorrhage or edema.[3-6] Patients were randomized into one of 5 different biweekly or monthly treatment groups or placebo.[3-6] A study protocol amendment related to safety resulted in discontinuation of ApoE4 carriers who had been receiving lecanemab 10 mg/kg every two weeks for 6 months or less due to observations of high risk of developing symptomatic ARIA-E.[3-6] Due to the change, the lecanemab 10 mg/kg every two weeks arm contained only 30% ApoE4 carriers and 70% ApoE e4 non-carriers.[3-6] All subjects with ARIA-E as assessed by MRI discontinued lecanemab per protocol.

Lecanemab 10 mg/kg biweekly dosing regimen was unable to show a statistically significant difference on the ADCOMS compared to placebo at 12 months.[4-6] An amyloid PET substudy was performed with 315 patients where 277 were evaluated at week 79 (see **Table 5**). Given the study's primary endpoint failure, the FDA statistical reviewers cautioned that all secondary endpoints should be considered exploratory.[5]

Study 301
A phase 3, randomized, multicenter, double-blind, placebo-controlled, parallel group confirmatory trial ("Clarity AD") evaluated the efficacy and safety of lecanemab 10 mg/kg IV every 2 weeks over 18 months in 1795 patients with early AD.[7] The primary efficacy endpoint was the change from baseline at 18 months in the CDR-SB score.[7] Change from baseline in the ADAS-Cog14 score, the ADCOMS, and the ADCS-MCI-ADL were secondary endpoints.[7] Efficacy analyses

were performed in the modified intention-to-treat population, which was defined as participants who underwent randomization that received at least one dose of lecanemab or placebo and who had a baseline assessment and at least one post-dose primary efficacy (CDR-SB) measurement.[4] A separate substudy was conducted to investigate amyloid burden on PET (n=698), tau pathology on PET (n=257), and AD CSF biomarkers (n=281).[7] Trial participants were required to have mild cognitive impairment as evidenced by an MMSE score of 22-30.[7]

At baseline, the mean CDR-SB score was 3.2, about 38% had mild dementia due to AD, and the rest were classified with MCI due to AD.[7] The patients ranged from 50-90 years of age (mean age 71 years). All patients had evidence of amyloid burden as confirmed by PET or CSF measurements of Aβ.[7] Almost 70% were ApoE4+ (carriers).[7] The mean MMSE score for participants was 25.5. About half the patients were on a medication for AD symptoms (ACHEIs, memantine, or both).[7] Over half (52%) of the patients identified as female, 77% White, 17% Asian, 12% Hispanic, and only 2% as Black.[7] The other baseline characteristics of the study participants were generally similar between trial groups.[7]

At 18 months, the adjusted least-squares mean change of the CDR-SB score from baseline favored lecanemab compared to placebo (MD -0.45; 95% CI, -0.67 to -0.23; P<0.001).[7] When separated by clinical subgroup, the reported mean difference from placebo in the CDR-SB score was -0.35 and -0.62 for MCI and mild AD, respectively. When reported by sex, the adjusted mean difference from placebo in the CDR-SB was -0.73 for males (statistically significant) but -0.20 for females (not statistically significant – via forest plot).[7] In the substudy of amyloid burden on PET, there was a change from baseline of -55.48 centiloids in the lecanemab group versus 3.64 centiloids in the placebo group (MD -59.15 centiloids; 95% CI, −62.64 to −55.60; P<0.001).[7] There were statistically significant changes in the other secondary outcome measures of ADAS-Cognitive subscale score (MD -1.44; 95% CI, -2.27 to -0.61), the ADCOMS (MD -0.05; 95% CI, -0.074 to -0.027,) , and the ADCS-MCI-ADL (MD 2.0; 95% CI, 1.2 – 2.8) for lecanemab-treated groups compared to placebo (P<.001 for all).[7] There is insufficient evidence to assess the clinical significance of these changes and whether changes in amyloid levels has an effect on cognitive decline.

Limitations: The FDA approved lecanemab based on one study that did not meet its own prespecified criteria for success and relied on a secondary surrogate endpoint that reviewers determined was reasonably likely to predict a clinical benefit. Study 301 was published after FDA approval and reported a modest but statistically significant benefit in reducing the CDR-SB score, but it fell short of the MCID threshold recognized in published literature. The clinical significance of less than half a point on an 18-point cognitive/functional clinical scale is unclear as previous studies have reported that 1 to 2 points represent the MCID in patients with mild AD.[53,59] Furthermore, it is unknown if the reported effects on cognition has an equal effect on women compared to men as there were between group differences in CDR-SB scores reported when results were analyzed by sex. 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 lecanemab has any benefit in moderate AD or if any reported benefit would be sustained if drug were discontinued. 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.[59] Longer, more robust trials are needed in order to provide definitive results in areas of clinical importance for individuals with early AD.[60, 61]

Clinical Safety:

For the phase 3 trial, the most common adverse events associated with the use of lecanemab were infusion reactions, ARIA-H (combined cerebral microhemorrhages, cerebral macrohemorrhages, and superficial siderosis), ARAI-E (edema/effusion), headache and falls.[7] Most of the infusion reactions were mild to moderate and occurred after administration of the first dose.[7] There were 6 (0.7%) deaths in the lecanemab group and 7 (0.8%) deaths in the placebo group, none of which were attributed to ARIA by the investigators.[7] For those patients who experienced ARIA-E, the majority (81%) had their first episode by the 11th dose of lecanemab.[7] In addition, of the 113 (12.6%) patients treated with lecanemab who developed brain edema, 25 (22%) developed symptoms.[7] There

were 126 (14%) serious adverse events in the lecanemab group compared to 101 (11.3%) in the placebo group.[7] Treatment-emergent adverse events occurred in 88.9% of lecanemab patients and in 81.9% of the placebo group.[7]

Table 3. Adverse Reactions[7]

	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)
Covid-19	64 (7.1)	60 (6.7)
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)

The FDA has issued a boxed warning for increased risk of ARIA, including symptomatic ARIA, in ApoE4 homozygotes compared to heterozygotes and noncarriers.[6] Testing for ApoE4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA.[6] Prescribers are instructed to obtain a recent (within one year) brain MRI prior to initiating treatment with lecanemab and ongoing MRIs prior to the 5th, 7th, and 14th infusions.[6] 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.[6] 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.[6] Asymptomatic patients with mild ARIA-E or ARIA-A may continue supervised dosing.[6] Lecanemab FDA labeling contains a warning to also monitor for infusion related reactions including flu-like symptoms, nausea, vomiting, and changes in blood pressure.[6] Long-term clinical outcomes including mortality have not been studied with lecanemab.

Comparative Endpoints:

Clinically Meaningful Endpoints:

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

Primary Study Endpoint:

1) Change in CDR-SB from baseline at 18 months

Table 4. Pharmacology and Pharmacokinetic Properties.[4,6]

Parameter	
Mechanism of Action	IgG1 monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid-beta
Oral Bioavailability	N/A
Distribution and Protein Binding	Vd=3.22 (3.15-3.28) L; no information available on protein binding
Elimination	No information on route of elimination; Clearance = 0.434 (0.420-0.451) L/day
Half-Life	5 to 7 days
Metabolism	Degraded by proteolytic enzymes

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

Table 5. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
Swanson CJ et al. [Study 201][3,5-7] Phase 2b, DB, PC, RCT	1. lecanemab (LEC) 10 mg/kg every 2 weeks* 2. Placebo (PBO) every 2 weeks *=also studied LEC in 2.5 mg biweekly, 5 mg biweekly and monthly, and 10 mg monthly	Demographics: Mean age: 71.3 years Male: 50% MCI due to AD: 64% Mild AD: 36% ApoE4+ (carriers): 1. 30% 2. 71% Baseline MMSE: 22 to 26 = 60% 27-30 = 40% Mean MMSE: 25.7 CDR-SB: 2.9 Mean ADCOMS: 0.38 ACHEI and/or memantine: 54% Race, ethnicity: Not reported Key Inclusion Criteria: -MCI due to AD or mild AD dementia -Memory impairment -Positive brain amyloid via PET or CSF assessment of t-tau/Aβ (1-42) -Age ≥50 to ≤90 years -MMSE score ≥22 (screening) and ≤30 (baseline) -BMI >17 and <35% -Naïve to or on stable dose (12 weeks) of AD medications (AChEI and/or memantine) Key Exclusion Criteria: -Non-AD cognitive impairment or dementia -Hx of transient ischemic attacks, stroke, or seizures within 12 months -Psychiatric diagnosis or symptoms, suicidal ideation, drug or alcohol abuse/dependence -Brain lesions (e.g. > 4 micro-hemorrhages, microhemorrhage, superficial siderosis) -Immunological disease (uncontrolled or requiring biologics) -Bleeding disorder -Abnormal labs/testing including: TSH, low Vit B12, prolonged QTc, or HIV+	ITT: 1. 161* 2. 247 *=includes only 10 mg/kg biweekly dosing cohort; total receiving LEC=609 Attrition: 1. 74** (46%) 2. 68 (28%) **=for all doses	Primary Endpoint: Mean change from baseline in the ADCOMS at 12 months (≥25%): -not statistically significant at all doses studied Secondary Endpoints: Change from baseline in brain amyloid beta PET Centiloid compared to PBO: Composite SUVR 1. -0.306 2. 0.004 MD -0.31 (p<0.001) PET Centiloid 1. -72.5 2. 1.0 MD -73.5 (p<0.001) Change from baseline in CDR-SB at week 79: NS Change from baseline ADAS-Cog14 at week 79: -Only 10 mg/kg biweekly dose had statistically significant finding: MD -2.31 (90% CI, -3.91 to -0.72; p=0.02)	NA NA	Discontinuation due to adverse event: LEC = 92* (15.1%) PBO = 15 (6.1%) SAE: LEC = 86* (14.1%) PBO = 43 (17.6%) TEAE LEC = 452* (74.2%) PBO = 216 (88.2%) Deaths: LEC = 5* (0.8%) PBO = 2 (0.8%) ARIA-H LEC = 65* (10.7%) PBO = 13 (5.3%) ARIA-E LEC = 46* (7.6%) PBO = 2 (0.8) *=for all LEC doses	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomization created by the IVRS. Baseline characteristics generally balanced except very low ApoE4 positive representation in lecanemab 10mg/kg biweekly group. Performance Bias: (Unclear) Identical vials with placebo injection dispensed by unblinded pharmacists. Detection Bias: (Unclear) All study personnel and subjects blinded with respect to the dose regimen (excluding pharmacists). Interim analysis conducted at 3-month intervals by unblinded external independent. statisticians. Protocol amended during study to discontinue ApoE4 carriers from lecanemab 10 mg/kg biweekly group. Attrition Bias: (High) Attrition in almost half of the high-dose lecanemab study arm discontinued treatment. Reporting Bias: (Low) Trial appeared to be conducted according to protocol and outcomes reported as pre-specified. Other Bias: (High) Funded by manufacturer; Most authors employed by manufacturer. **Applicability**: Patient: Race/ethnicity of participants not reported Intervention: Appropriate based on earlier phase testing Comparator: Placebo appropriate for safety/efficacy; aducanumab 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: US (80%), Canada (5%), Western Europe (9%), Asia (6%)

		-Uncontrolled T1DM or T2DM, HTN, CVD -Malignant neoplasms last 3 years -Severe visual or hearing impairment -GDS score ≥8						
2.van Dyck et al.[4] Phase 3, DB, PC, RCT	1. lecanemab 10 mg/kg every 2 weeks 2. Placebo	Demographics: Female:52% Mean age: 71 Race/ethnicity: -White 77% -Black 2% -Asian 17% -Other 4% Concomitant AD meds: 52-53% ApoE4+ (Carrier): 68-69% -Heterozygous carrier: 53% -Homozygous carrier: 15% CDR-SB: 3.2 Mean MMSE score: 25.5 MCI due to AD: 61-62% Mild AD dementia: 38% Key Inclusion Criteria: -Age 50-90 years old, -MCI due to AD w/mild dementia -Amyloid pathology confirmed by amyloid PET or CSF assessment of tau/Aβ (1-42) ratio -MMSE score of 22-30 -BMI 17 to 35% -If on approved concurrent AD therapy (e.g. memantine, AChEI or both) must be stable for 12 weeks before baseline Key Exclusion Criteria: -Any neurological condition that may be contributing to cognitive impairment above and beyond AD -history of TIAs/stroke or seizures within 12 months of screening -any interfering psychiatric diagnosis or symptoms -drug or alcohol abuse within prior 2 years -any uncontrolled medical condition that could affect safety or study assessment -contraindications to MRI scanning -clinically significant lesions on brain MRI at screening that could indicate a dementia	ITT 1. 898 2. 897 mITT: 1. 859 2. 875 Attrition: 1. 169 (18.8%) 2. 140 (15.6%)	Primary Endpoint: Change in CDR-SB from baseline at 18 months LEC: 1.21 PBO: 1.66 MD -0.45 (95% CI, −0.67 to −0.23; P<0.001) Secondary Endpoints: Change from baseline to 18 mo in amyloid burden on PET (centiloids) LEC: -55.48 PBO: 3.64 MD: −59.12 (95% CI, −62.64 to −55.60; P <0.001) Change from baseline to 18 mo in the ADAS-cog14 score: LEC: 4.14 PBO: 5.58 MD: −1.44 (95% CI, −2.27 to −0.61; P <0.001) Change from baseline to 18 mo in the ADCOMS LEC: 0.164 PBO: 0.214 MD −0.050 (95% CI, −0.074 to −0.027; P <0.001) Change from baseline to 18 mo in the ADCS-MCI-ADL score LEC: −3.5 PBO: −5.5	NA NA	Discontinuation due to adverse event: 1. 62 (6.9%) 2. 26 (2.9) SAE: 1. 126 (14.0%) 2. 101 (11.3%) TEAE 1. 798 (88.9%) 2. 735 (81.9%) Deaths: 1. 6 (0.7%) 2. 7 (0.8%) Infusion reactions: 1. 237 (26.4%) 2. 66 (7.4%) ARIA-H 1. 155 (17.3%) 2. 81 (9%) ARIA-E 1. 113 (12.6%) 2. 15 (1.7%) Headache 1. 100 (11.1%) 2. 73 (8.1%) Fall 1. 93 (10.4%) 2. 86 (9.6%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias:(Low) Centralized, computer-generated randomization scheme reviewed and approved by an independent statistician Performance Bias: (Unclear) High rates of infusion reactions in drug group versus placebo with blinding potentially broken during trial. Detection Bias: (Low) independent data and safety monitoring board experts in Alzheimer's disease and statistics reviewed unblinded safety data; independent medical monitoring team that were unaware of the trial-group assignments reviewed ARIA, infusion related reactions, and hypersensitivity reactions; clinical assessment raters were unaware of the safety assessments and the trial-group assignments. Attrition Bias: (High) dropout rate >10%; mITT for those who discontinued drug but remained in trial. Reporting Bias: (Low) Study protocol available and appeared to be followed with all pre-specified primary and secondary outcomes reported. Other Bias: (High) Funded by manufacturer; Most authors serve as consultants for manufacturer. **Applicability**: Patient: 70% patients screened were ineligible; Extensive exclusions of patients with comorbidities. People who identified as black or of other racial and ethnic groups were under-represented. Intervention: Dose and comprehensive safety monitoring (adverse events, vital signs, physical examinations, clinical laboratory variables, and 12-lead electrocardiograms) at specific intervals

		diagnosis besides AD -any interfering medications within prior 6 mos (immunosuppressants, immunoglobulins) -prior exposure to lecanemab -HIV+ -low vitamin B12 -GDS score ≥8 at screening -Pregnant or breastfeeding females		MD 2.0 (95% CI, 1.2 to 2.8; P <0.001)				during treatment appropriate based on previous Phase 2 studies. Comparator: Placebo appropriate given few standard treatment options that delay, halt, or reverse AD. Outcomes: CDR-SB not a standard outcome measure in AD; amyloid plaque reduction is a surrogate endpoint that does not have clear effects on cognition; no outcomes such as behavioral symptoms or time to institutionalization were studied. Setting: Sites in North America, Europe, Asia, and Australia
Abbreviations : ACHEI=acetylcholinesterase inhibitor; ADCS-MCI-ADL=Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale for Mild Cognitive Impairment; AD=Alzheimer's disease; ADCOMS= Alzheimer's Disease Composite Score; ARIA= amyloid-related imaging abnormalities; ApoE4=apolipoprotein E4;ARIA-E=ARIA with edema or effusions; ARIA-H ARIA with hemorrhage; ARR = absolute risk reduction; BMI=body mass index; CDR=clinical dementia rating; CDR-SB=CDR–Sum of Boxes; CI = confidence interval; CSF=cerebrospinal fluid; CVD=cardiovascular disease; GDS=Geriatric depression scale; Hx=history; ITT = intention to treat; HTN=hypertension; IVRS=Interactive Voice Response System; LEC=lecanemab; MAB=monoclonal antibody; MCI=mild cognitive impairment; MD=mean difference; mg=milligram; MMSE=Mini–Mental State Examination; mo=months; MRI=magnetic resonance imaging; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PET=Positron Emission Tomography; PBO=placebo; PP = per protocol; SUVR=standardized uptake value ratio; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; TIA=transient ischemic attack; TSH=thyroid stimulating hormone; Tx=treatment; vit=vitamin								

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
donepezil HCl	DONEPEZIL HCL ODT	TAB RAPDIS	PO	Y
donepezil HCl	ARICEPT	TABLET	PO	Y
donepezil HCl	DONEPEZIL HCL	TABLET	PO	Y
galantamine HBr	GALANTAMINE ER	CAP24H PEL	PO	Y
galantamine HBr	RAZADYNE ER	CAP24H PEL	PO	Y
galantamine HBr	GALANTAMINE HBR	TABLET	PO	Y
memantine HCl	MEMANTINE HCL ER	CAP SPR 24	PO	Y
memantine HCl	NAMENDA XR	CAP SPR 24	PO	Y
memantine HCl	MEMANTINE HCL	SOLUTION	PO	Y
memantine HCl	MEMANTINE HCL	TAB DS PK	PO	Y
memantine HCl	NAMENDA	TAB DS PK	PO	Y
memantine HCl	MEMANTINE HCL	TABLET	PO	Y
memantine HCl	NAMENDA	TABLET	PO	Y
memantine HCl/donepezil HCl	NAMZARIC	CAP SPR 24	PO	Y
memantine HCl/donepezil HCl	NAMZARIC	CAP24 DSPK	PO	Y
rivastigmine	EXELON	PATCH TD24	TD	Y
rivastigmine	RIVASTIGMINE	PATCH TD24	TD	Y
rivastigmine tartrate	RIVASTIGMINE	CAPSULE	PO	Y
aducanumab-avwa	ADUHELM	VIAL	IV	N
donepezil HCl	ADLARITY	PATCH TDWK	TD	N
galantamine HBr	GALANTAMINE HYDROBROMIDE	SOLUTION	PO	N
lecanemab-irmb	LEQEMBI	VIAL	IV	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to June 22, 2023

1. donepezil.mp. or Donepezil/4901
2. galantamine.mp. or Galantamine/2583
3. rivastigmine.mp. or Rivastigmine/2220
4. memantine.mp. or Memantine/4410
5. aducanumab.mp./446
6. lecanemab.mp./114
7. Alzheimer disease.mp. or Alzheimer Disease/125290
8. alzheimers.mp./166073
9. 1 or 2 or 3 or 4 or 5 or 6/11885
10. 7 or 8/197593
11. 9 and 10/6469
12. limit 11 to (english language and full text and humans and yr="2021 -Current")/144

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LEQEMBI® safely and effectively. See full prescribing information for LEQEMBI®.

LEQEMBI® (lecanemab-irmb) injection, for intravenous use
Initial U.S. Approval: 2023

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

Monoclonal antibodies directed against aggregated forms of beta amyloid, including LEQEMBI, can cause amyloid related imaging abnormalities (ARIA), characterized as ARIA with edema (ARIA-E) and ARIA with hemosiderin deposition (ARIA-H). ARIA is usually asymptomatic, although rarely serious and life-threatening events can occur. Serious intracerebral hemorrhage greater than 1 cm have occurred in patients treated with this class of medications. (5.1, 6.1)

ApoE ε4 Homozygotes
Patients treated with this class of medications, including LEQEMBI, 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 of LEQEMBI for the treatment of Alzheimer's disease and potential risk of serious adverse events associated with ARIA when deciding to initiate treatment with LEQEMBI. (5.1, 14)

RECENT MAJOR CHANGES

Boxed Warning	7/2023
Indications and Usage (1)	7/2023
Dosage and Administration (2.3)	7/2023
Contraindications (4)	7/2023
Warnings and Precautions (5.1, 5.2, 5.3)	7/2023

INDICATIONS AND USAGE

LEQEMBI is indicated for the treatment of Alzheimer's disease. Treatment with LEQEMBI 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. (1)

DOSAGE AND ADMINISTRATION

- Confirm the presence of amyloid beta pathology prior to initiating treatment. (2.1)
- The recommended dosage is 10 mg/kg that must be diluted then administered as an intravenous infusion over approximately one hour, once every two weeks. (2.2)
- Obtain a recent baseline brain MRI prior to initiating treatment. (2.3, 5.1)
- Obtain an MRI prior to the 5th, 7th, and 14th infusions. If radiographically observed ARIA occurs, treatment recommendations are based on type, severity, and presence of symptoms. (2.3, 5.1)
- Dilution in 250 mL of 0.9% Sodium Chloride Injection, USP, is required prior to administration. (2.4)
- Administer as an intravenous infusion over approximately one hour via a terminal low-protein binding 0.2 micron in-line filter. (2.5)

DOSAGE FORMS AND STRENGTHS

Injection:
- 500 mg/5 mL (100 mg/mL) solution in a single-dose vial (3)
- 200 mg/2 mL (100 mg/mL) solution in a single-dose vial (3)

CONTRAINDICATIONS

LEQEMBI is contraindicated in patients with serious hypersensitivity to lecanemab-irmb or to any of the excipients of LEQEMBI. (4)

WARNINGS AND PRECAUTIONS

- Amyloid Related Imaging Abnormalities (ARIA): Enhanced clinical vigilance for ARIA is recommended during the first 14 weeks of treatment with LEQEMBI. Risk of ARIA, including symptomatic ARIA, was increased in apolipoprotein E ε4 homozygotes compared to heterozygotes and noncarriers. 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 administered as clinically indicated. Consider pre-medication at subsequent dosing with antihistamines, non-steroidal anti-inflammatory drugs, or corticosteroids. (5.2)

ADVERSE REACTIONS

Most common adverse reactions (at approximately 10% and higher incidence compared to placebo): infusion-related reactions, amyloid related imaging abnormality-microhemorrhages, amyloid related imaging abnormality-edema/effusion, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eisai Inc. at 1-888-274-2378 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 7/2023

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	Function, symptoms, disease progression, quality of life, morbidity, mortality
Timing	Any duration
Setting	Outpatient

Monoclonal Antibodies for Alzheimer's Disease

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
Aducanumab	90 days prior to Infusion 1	See Prescribing Information for dosing recommendations and for interruptions in therapy due to ARIA.	Every 4 Weeks
	--		
	--		
	28 days prior to Infusion 7		
	28 days prior to Infusion 12		
	Annually		
Lecanemab	At least 28 days prior to infusion 1 (no longer than 1 year)		Every 2 Weeks
	28 days prior to Infusion 5		
	28 days prior to Infusion 7		
	28 days prior to infusion 14		

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
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

Approval Criteria		
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 90 days 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
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 the patient been screened to ensure they are not currently receiving anticoagulant or antiplatelet therapy (excluding aspirin 81 mg)?	**Yes:** Go to #11.	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
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? Patient 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

Renewal Criteria		
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 there documentation that, compared to baseline assessment, therapy has resulted in: • cognitive or functional improvement **OR** • disease stabilization **OR** • a reduction in 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: 10/23 (DE);10/21(DE)
Implementation: 11/1/23; 1/1/22