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

Date of Review: October 2021

Date of Last Review: September 2015
Literature Search: 01/01/16 – 07/01/21

Generic Name: aducanumab-avwa

Brand Name (Manufacturer): Aduhelm™ (Biogen)

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

Purpose for Class Update:
The purpose of this class update is to evaluate place in therapy for aducanumab, a new monoclonal antibody (MAB) reported to reduce aggregated soluble and insoluble amyloid beta plaques in patients with mild Alzheimer's disease (AD). Aducanumab is the first MAB approved for therapy in patients with mild AD.

Research Questions:
1. What is the comparative efficacy or effectiveness of therapies for AD?
2. What is the comparative safety of therapies for AD?
3. Are there any subgroups (i.e., based on age, gender, race, ethnicity, comorbidities, disease duration or severity) that would benefit or be harmed from drugs for AD?
4. Is aducanumab safer or more effective than currently available agents for the treatment of patients with mild AD?

Conclusions:
- No new evidence of comparative efficacy or effectiveness of acetylcholinesterase inhibitors (ACHEIs; including donepezil, galantamine, and rivastigmine) or the N-methyl-d-aspartate (NMDA) antagonist memantine has been published since the last AD class review.
- In mild to moderate AD patients, there was low- to moderate-quality evidence that ACHEIs improved outcomes of cognition (Mean Mini-Mental State Examination (MMSE) or Alzheimer's Disease Assessment Scale-Cognition (ADAS-Cog) change: Standardized Mean Difference (SMD) 0.24-0.52; number needed to benefit for >4-pt ADAS-cog improvement = 5-11).[1]
- In moderate to severe AD patients:
    - ACHEI monotherapy showed modest improvement in cognition endpoints for MMSE or Severe Impairment Battery (SIB): SMD 0.29 compared to placebo) (low-quality evidence).[1]
    - Memantine 20 mg daily (with or without concomitant ACHEI) showed modest improvement in: clinical global rating score (SMD -0.21; 95% CI -0.14 to -0.30); cognitive function (SMD -0.27; 95% CI -0.34 to -0.21); activities of daily living (SMD -0.16; 95% CI -0.24 to -0.09); and behavior and mood (SMD -0.14; 95% CI -0.21 to -0.08) versus placebo (high-quality evidence).[24]

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- In severe AD patients, there was low-quality evidence that donepezil improved outcomes of function (mean AD Cooperative Study-Activities of Daily Living Inventory (ADCS-ADL) change, SMD, 0.18 [95% CI, 0.03 to 0.32]) and clinical impression of change (likelihood improved: 38% vs. 28% (up to 10 mg/day); Absolute Risk Difference (ARD), 10% [95% CI, 5% to 15%]; NNTB, 10 [95% CI, 7 to 20] over 24-26 weeks) compared to placebo.[1]
- In mild to moderate AD there was increased risk of severe adverse events (SAEs) with donepezil therapy versus placebo (10.7% vs. 8.7%, respectively).[1]
- There was low quality evidence of increased risk of withdrawals due to adverse events with donepezil therapy compared to placebo in severe/moderate to severe AD patients and in mild to moderate AD patients treated with galantamine compared to placebo. [1]
- The magnitude of benefit with ACHEIs for improvements in cognition and function was relatively small with standardized mean differences [SMD] between 0.20 to 0.40 for cognition and roughly 0.20 for function.
- Aducanumab was approved based on 2 identically designed, multicenter, randomized, double-blind, placebo-controlled, parallel-group, unpublished phase 3 trials with incongruent results. Both trials were terminated early due to futility. The primary outcome was change from baseline in the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score compared to placebo at week 78, and approximately 50% of the patients were missing the Week 78 time point assessment. [2,3]
- In study 302, the low-dose aducanumab group reported no statistically significant difference in CDR-SB score reduction and no significant improvements in secondary outcome measures compared to placebo at week 78. The high-dose aducanumab group reported a statistically significant change from baseline in CDR-SB score compared to placebo (-0.39 points; p=0.0120) but the results were not clinically significant. The high dose group also reported statistically significant changes in the secondary endpoints of MMSE scores (0.6; p=0.0493), ADAS-Cog 13 score (-1.4; p=0.0097), and ADCS-ADL-Mild Cognitive Impairment (MCI) score (1.7; p=0.0006). [2,3] No compelling evidence was found to suggest any of these relatively small differences were clinically significant.
- The aducanumab studies had numerous limitations including:
    - Early study termination
    - Post-hoc analyses for re-evaluation of endpoints
    - Multiple post-hoc subgroup analyses
    - Missing data
    - Inconsistency
    - Surrogate endpoints with no direct correlation to clinical improvement
- In study 301, there were no statistically significant differences in primary or secondary endpoints for either the low-dose or high-dose aducanumab groups compared to placebo at 78 weeks. The high dose aducanumab groups reported numerically inferior results compared to placebo.[2,3]
- It has not been demonstrated that removal of beta amyloid plaque results in any clinically meaningful improvements (or slows decline) in AD symptoms, function, or cognition as no amyloid lowering agent has shown a definitive clinical benefit associated with changes in beta-amyloid levels.[2,13]
- Aducanumab treatment at 10 mg/kg resulted in an increased incidence of amyloid-related imaging abnormalities (ARIA) including brain microhemorrhage and edema compared to placebo (41% vs. 10%, respectively).[2,3] There is insufficient evidence to verify long-term safety of aducanumab or in patients with pre-existing risk factors for bleeding, including concomitant medications that could increase the risk for bleeding.[2-4]
- There is insufficient evidence that use of aducanumab in patients with AD has any impact on symptoms, cognitive or functional improvement, quality of life, or disease progression.[3]
- There is no comparative efficacy or safety data for aducanumab versus other agents used to treat AD. The required post-marketing study to verify and describe the clinical efficacy of aducanumab compared to an appropriate control for the treatment of AD is expected to be completed in 2030.[2,4,30]

Recommendations:

- Maintain aducanumab as a non-preferred agent in the Alzheimer's disease drugs PDL class.
- Implement PA criteria for aducanumab to ensure appropriate use.
- Costs were evaluated in executive session and donepezil (tablets and rapid tablets), rivastigmine capsules, memantine ER sprinkle capsules, and memantine/donepezil combinations were made preferred.

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 September 2015. Previous evaluations concluded that there remains insufficient evidence for the treatment of AD beyond 6 months. There was moderate quality evidence that cholinesterase inhibitors can alleviate AD symptoms but no strong evidence that one agent was more efficacious or safer than others. It was also found that while ACHEIs and memantine have demonstrated modest but persistent improvements in cognition, activities of daily living, and behavior, none of the approved medications had been shown to stop or reverse the underlying process or any impact on important clinical outcomes such as mortality, disability, or institutionalization in patients with moderate-to-severe AD. There was low quality evidence that cholinesterase inhibitors can reduce neuropsychiatric symptoms in patients with AD but no effect with memantine. Lastly, there was moderate quality evidence of a small but significant benefit of combination therapy with cholinesterase inhibitors and memantine on behavior and cognitive functions, but no difference in activities of daily living or serious adverse events. Therefore, no new comparative efficacy or safety data resulted in changes to the PDL at that time.
- Currently, a variety of ACHEIs and memantine formulations are available on the preferred drug list (PDL) that do not require prior authorization (PA) (See **Appendix 1**).

Background:

Alzheimer's dementia is a progressive disease of neurological degeneration and memory impairment that primarily affects the elderly.[5] AD is characterized by deterioration of cognitive and reasoning skills, poor coordination and muscle function, personality changes, and an incapability of autonomous self-care.[5] Common neurological manifestations of AD include 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.[5] Alzheimer's dementia is the most common form of dementia and accounts for 60-80% of all dementia cases.[5] Prevalence increases with age as roughly 1%-2% in adults up to age 65 years have AD, but prevalence may be as high as 30% to 50% by age 85.[6] In the United States (US) alone, roughly 17% of individuals between the ages of 75 and 84 years have AD.[6,7] At current rates, it is predicted that America will experience a 35% increase in dementia by 2030, and prevalence will triple by 2050.[6]

Alzheimer's dementia is typically diagnosed based on a combination of clinical findings, medical history, and brain imaging.[5-7] Evaluation involves ascertainment of medical history from the patient and family member (or caregiver) along with a cognitive and neurologic examination.[6,7] Late-onset AD (LOAD) affects the majority (greater than 95%) of AD patients and typically occurs after 65 years of age, while early-onset AD (EOAD) tends to begin at 45 to 65 years of age.[6] Patients suspected to have AD often present with short-term memory loss in the early stage which may be accompanied by other cognitive deficits such as visuospatial issues and anomia.[7] Alzheimer's dementia has a slow onset and progresses gradually over many months or years.[7] Beta-amyloid plaques and neurofibrillary tangles have been implicated in the pathophysiology of AD and are believed to play a role in the disruption of neuron signaling.[8] Accumulation of beta-amyloid protein observed through Positron Emission Tomography (PET) neuroimaging may reveal brain atrophy in the mesial temporal lobe of the cerebral cortex.[8] Elevated cerebral spinal fluid (CSF) tau and intracellular deposits of tau protein in the cortical region may also be biomarkers of neuronal degeneration.[8] In the theoretical "amyloid cascade hypothesis," cognitive impairment follows a series of events where beta-amyloid deposited in the brain stimulates tau phosphorylation, neurofibrillary tangle formation, synapse degradation, then neuron destruction and death.[9] The ε4 allele of the Apolipoprotein E gene (APOE4)

is a strong genetic risk factor for AD may be associated with faster beta amyloid deposition, earlier onset of AD, and an increased risk of AD symptoms.[6,10] Although estimates vary between studies and ethnicities, the APOE4 allele is usually present in more than 50% of AD patients but found in only about 15% of healthy older controls.[8,10] Attempts to screen for AD and related dementia have been unable to show a clear benefit on disease prevention or in measures of health-related quality of life.[11,12]

Current FDA-approved therapies for AD include ACHEIs and the NMDA antagonist memantine.[7] These agents are typically used in mild to moderate dementia to alleviate AD symptoms.[7,8] ACHEIs are intended to increase acetylcholine in the central nervous system via suppression of the metabolizing enzyme acetylcholinesterase.[7] Memantine blocks the excitatory effects of glutamate by the preferential binding to NMDA receptor channels to facilitate synaptic transmission, neuronal growth and differentiation.[7] Both ACHEIs and NMDA antagonists have revealed modest treatment effects in various stages of AD.[7] 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 [7]

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 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	
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 extended release (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

Abbreviations: ACHEI=acetylcholinesterase inhibitor; AD=Alzheimer's dementia; ER= extended release; max =maximum; ODT=orally disintegrating tablet

Over the past 15 years, most AD drug therapy research has focused on immunotherapy targeted at accumulation of beta amyloid plaques.[13] Several MAB drugs have been developed to either decrease amyloid beta production, hinder beta-amyloid aggregation, or increase beta-amyloid clearance but none of these agents have been able to demonstrate a definitive clinical benefit associated with changes in beta-amyloid levels.[13] In addition, studies with amyloid modifying therapies and specifically beta-amyloid targeting MABs (e.g. bapineuzumab and aducanumab) have revealed their own unique safety risks collectively known as ARIA.[14] ARIA may be observed in patients who have undergone a MAB infusion as a result of anti-Aβ autoantibody development in the CSF.[14] Magnetic resonance imaging (MRI) with ARIA findings may reveal brain swelling or microhemorrhages referred to as ARIA-edema (ARIA-E) and ARIA-hemorrhage (ARAI-H), respectively.[14,15] These ARIA may present with headache, confusion, and other neuropsychiatric abnormalities and it is usually observed between the first and third therapy infusion.[15] Not all AD patients develop ARIA after amyloid modifying therapy, but a number of drug trials have suggested that efficacy and side effect profiles may differ between APOE4 carriers and non-carriers.[10] The link between APOE4 carriers and increased risk of beta amyloid plaque-related hemorrhage and vascular damage has been proposed.[10] There is no consensus on the most effective method to classify MRI findings for ARIA although some studies have suggested various methods to monitor and evaluate ARIA-E findings through reproducible scales.[16] Nonetheless, lack of clinical benefit and early biomarkers of ARIA-like events has led many manufacturers to search for alternative drug targets. [13,15]

Clinically important outcomes in AD include mortality, cognitive function, quality of life, functional performance in activities of daily living (ADL), behavioral disturbances, serious adverse events, and study withdrawal due to an adverse event. 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 MMSE is a commonly used dementia scale (30 points possible, higher is better, MCID defined as 1 to 3 points) which generally separates AD into 3 categories: mild dementia (19-26 points), moderate dementia (10-18 points), and severe dementia (<10 points). In mild AD, studies have used the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) which measures cognitive and functional impairment in AD. 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.[2] A qualified rater uses the interview data and clinical judgment to assign scores for each domain which may range from none = 0, questionable = 0.5, mild = 1, moderate = 2 to severe = 3.[2] Scores from each domain are summed to provide the CDR-SB value from 0 (normal) to 18 (severe dementia).[2] A CDR-SB score in the range of 0.5-4.0 may be interpreted as questionable cognitive impairment to very mild dementia, while mild dementia is typically associated with a CDR-SB score range of 4.5-9.0. 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.[2] An increase of 1- to 2-points on the CDR-SB was found to be clinically meaningful by the National Alzheimer's Coordinating Centers (NACC) Uniform Data Set (UDS).[17] 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 11-question Alzheimer's Disease Assessment Scale-Cognition (ADAS-Cog11; 70 points possible, lower score better; MCID defined as at least 3 points), 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).[1,18-21]

Historically, FDA guidance required that clinical interventions for AD trials demonstrate efficacy in cognitive and/or functional domains with a clinically meaningful treatment effect determined by individual patient feelings, functional improvements, and survival.[22] To assist industry in proper clinical trial design and selection of appropriate outcome measures for various stages of early AD, the FDA developed a classification system comprised of 4 stages: Stage 1 (pathophysiologic changes of AD but no evidence of clinical impact), Stage 2 (pathophysiologic changes of AD, subtle or more apparent detectable abnormalities

on sensitive neuropsychological measures, and mild but detectable functional impairment), Stage 3 (pathophysiologic changes of AD, subtle or more apparent detectable abnormalities on sensitive neuropsychological measures, and mild but detectable functional impairment), and Stage 4 (overt dementia).[2,22] Although the FDA typically determines whether benefit outweighs risk, MCID thresholds have not always been required prior to approval.[22] 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, to date, do not have well-established clinical significance.[23]

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, 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.

New Systematic Reviews:
Agency for Healthcare Research and Quality
A 2020 systematic review commissioned by AHRQ was conducted to evaluate the comparative effectiveness, benefits, and harms of prescription drugs and supplements for cognition, function, and behavioral and psychological symptoms for patients in various stages of AD[1]

Eligible studies included RCTs, nonrandomized controlled clinical trials, observational studies, and systematic reviews.[1] Evidence was searched through March 2019.[1] There were 56 unique, low or medium risk-of-bias (ROB) trials that evaluated the efficacy and harms of prescription drugs or supplements for cognition, function, health-related quality of life (QoL), and harms in AD.[1] Interventions included various ACHEIs versus placebo, different doses of ACHEIs, memantine versus placebo, supplements versus placebo, comparative studies of prescription drugs, and comparisons between prescription drugs and supplements.[1] Most of the trials were between 24- and 26- weeks duration.[1]

Cognitive outcomes were generally measured by mean changes from baseline on a cognitive battery (> 4-point improvement in ADAS-Cog) or the MMSE.[1] Functional improvement outcomes were assessed by mean changes in Alzheimer's Disease Cooperative Study—Activities of Daily Living (ADCS-ADL) and Disability Assessment for Dementia (DAD).[1] Improvement was analyzed by a variety of global change measures such as the Clinician's Interview-Based Impression of Change with caregiver input [CIBIC-Plus] or Clinical Global Impression of Improvement [CGIC]).[1] The CGIC rating used a 7-point Likert-type scale where change from baseline is rated as marked improvement (1), moderate improvement (2), minimal improvement (3), no change (4), minimal worsening (5), moderate worsening (6), marked worsening (7).[1]

Overall, trials of roughly 6 months duration reported benefits with ACHEI treatment compared to placebo regardless of AD severity at baseline.[1] Evidence was insufficient to draw conclusions about comparative effectiveness or harms between FDA-approved pharmacotherapy agents (donepezil, galantamine,

rivastigmine, and/or memantine) used for the treatment of mild, moderate or severe AD.[1] Overall, ACHEIs were slightly better than placebo for improvements of cognition in adults with mild to moderate and moderate to severe AD, and individually produced small improvements in cognition, function, and clinical impression of change.[1] However, standard doses may increase serious adverse events and withdrawals due to adverse events.[1] The magnitude of benefit of ACHEIs for improvements in cognition and function was relatively small with standardized mean differences between 0.20 to 0.40 for cognition and roughly 0.20 for function.[1]

Cognition

In mild to moderate AD patients, there was low-quality evidence for donepezil and galantamine, and low- to moderate-quality evidence that rivastigmine were associated with improved cognition compared to placebo. Absolute changes compared to placebo for individual scales and drugs are listed below:

- Donepezil, MMSE change: Standardized mean difference [SMD] 0.30 [95%CI, 0.16 to 0.44]; 4 trials, n=806 ; low-quality evidence
- Galantamine, $\geq$ 4-point ADAS-Cog improvement: ARD 17% [95% CI, 10% to 25%]; NNTB, 6 [95% CI, 4 to 10]; 1 trial, n=653; low-quality evidence
- Rivastigmine 12 mg/day PO or 9.5 mg/day patch, MMSE change: SMD 0.24 [95% CI, 0.14 to 0.34]; 4 trials, n=2,439; low quality evidence
- Rivastigmine 12 mg/day oral or 9.5 mg/day patch, $\geq$ 4-point ADAS-Cog improvement: ARD, 8% [95% CI, 4% to 11%]; NNTB, 13 [95% CI, 9 to 25]; 3 trials, n=1819; moderate-quality evidence.[1]

Evidence was insufficient to draw conclusions about changes in cognition related to memantine therapy with or without a ACHEI.[1] In patients with moderate to severe AD, similar changes in mean MMSE scores were noted with donepezil therapy compared to placebo (SMD 0.29 [95% CI, 0.17 to 0.40]; 4 trials, n=1102) and improvements in SIB were reported with memantine added to ACHEI (SIB change: MD, 0.27 [95% CI, 0.12 to 0.42]; 2 trials, n=1081).[1]

Function

In mild to moderate AD patients, there was low-quality evidence from 4 RCTs (n=2979) that rivastigmine 12 mg daily orally or 9.5 mg per day patch resulted in functional improvements compared to placebo as demonstrated by a mean ADCS-ADL change (SMD, 0.21 [95% CI, 0.09 to 0.33]; 1 trials, n=782), and mean DAD change (SMD, 0.19 [95% CI, 0.03 to 0.37]); 1 trial, n=536).[1] There was insufficient evidence to detect functional improvements in trials with donepezil, galantamine, or memantine.[1] For patients with severe AD, there was low quality evidence that donepezil up to 10 mg daily was associated with functional improvements in the mean ADCS-ADL scale compared to placebo (SMD, 0.18 [95% CI, 0.03 to 0.32]; 3 trials, n=733). [1]

Clinical Impression of Change

There was moderate-quality evidence that more patients on donepezil therapy compared to placebo had statistically significant improvements in the Clinical Impression of Change score (ARD, 12% [95% CI, 8% to 16%]; NNTB, 8 [95% CI, 6 to 13]; 4 trials, n=1585) for patients with mild to moderate AD.[1] The Clinical Impression of Change score change was also improved in severe or moderate to severe AD patients treated with donepezil compared to placebo (38% vs. 28%; ARD, 10% [95% CI, 5% to 15%]; NNTB, 10 [95% CI, 7 to 20]; 4 trials, n=1152; low-quality evidence).[1] In mild to moderate AD patients, there was low-quality evidence that more patients on rivastigmine therapy had a 4-point or more improvement in the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) score versus placebo (ARD, 10% [95% CI, 7% to 14%]; NNTB, 10 [95% CI, 7 to 14]; 4 trials, n=2201) as did memantine monotherapy (SMD -0.27 [95% CI, -0.49 to -0.05]). [1] A similar finding favored both rivastigmine and memantine (plus an ACHEI) versus placebo in patients with moderate to severe AD. [1]

Serious Adverse Effects

Low quality evidence from 8 RCTs (n=2521) showed that donepezil up to 10 mg daily was associated with an increased risk of serious adverse events compared to placebo in severe or moderate to severe AD (10.7% vs. 8.7%; ARD, 2% [95% CI, -0.3 to 4.3]; NNTH, 50 [95% CI, NNTH 23 to NNTB 333]; RR, 1.32 [95% CI, 1.03 to 1.68]).[1]

Withdrawals due to Adverse Effects

Low-quality evidence from 7 RCTs (n=1559) showed that donepezil up to 10 mg daily, galantamine, and rivastigmine were each associated with an increased risk of withdrawals due to adverse events compared to placebo in different subgroups of AD patients:

- donepezil in severe or moderate to severe AD: ARD, 4.5% [95% CI, 1.5 to 7.6]; NNTH, 23 [95% CI, 14 to 67]; RR, 1.54 [95% CI, 1.13 to 2.10]; 1 trial, n=653
- galantamine in severe or moderate to severe AD: ARD, 9.2% [95% CI, 4 to 14.4]; NNTH, 11 [95% CI, 7 to 25]; RR, 2.04 [95% CI, 1.27 to 3.28]; 1 trial, n=653
- rivastigmine 12 mg/day oral or 9.5 mg/day patch in mild to moderate AD: ARD, 5.8% [95% CI, 3.7 to 8]; NNTH, 17 [95% CI, 13 to 27]; RR, 1.88 [95% CI, 1.35 to 2.61]; 5 trials, n=2836.[1]

Quality of Life

There was insufficient evidence for pharmacotherapy interventions associated with improvements in quality of life for AD patients.

Table 2 summarizes the findings for most outcome comparisons between prescription drugs and placebo. The strength of evidence was generally graded as insufficient to low for most domains (low to moderate evidence reported below).

Table 2. Summary of findings for primary outcomes: Prescription Drugs Versus Placebo in Alzheimer's Dementia Populations[1]

Domain	Drug vs placebo	AD population	Outcome/Results	Number of Trials/patients	Quality/Strength of Evidence
Cognition	All ACHEI	Mild to moderate	Mean MMSE or ADAS-Cog change: SMD 0.24-0.52; Likelihood >4-pt ADAS-Cog improvement: Number needed to Benefit (NNTB) 5-11	-Donepezil: 18 trials, n=4742 -Galantamine 2 trials, n=1060 -Rivastigmine: 5 trials, n=3674	Low
		Moderate to severe	MMSE or SIB: SMD 0.29		
	Donepezil	Mild to moderate	Mean MMSE change: SMD, 0.30 [95% CI, 0.16 to 0.44])	4 trials, n=806	Low
		Moderate to severe	Mean MMSE change: SMD, 0.29 [95% CI, 0.17 to 0.40])	4 trials, n=1102	Low
	Galantamine (24-32 mg/d orally)	Mild to moderate	Likelihood >4-point ADAS-Cog improvement: favors galantamine (ARD Range: 14%-17% [95% CI, 7% to 25%]; NNTB, 6 to 7 over 26 weeks	1 trial, n=653	Low
	Rivastigmine (12 mg/d orally or 9.5 mg/d patch)	Mild to moderate	-Mean MMSE change: SMD, 0.24 [95% CI, 0.14 to 0.34] -Likelihood >4-point ADAS-Cog improvement: favors rivastigmine (25% vs. 17%; ARD, 8% [95% CI, 4% to 11%]; NNTB, 13 [95% CI, 9 to 25]; RR, 1.47 [95% CI, 1.22 to 1.79]	4 trials, n=2439 3 trials, n=1819	Low Moderate
	Memantine with ACHEI	Moderate to severe	Mean SIB change favors add-on memantine: MD, 0.27 [95% CI, 0.12 to 0.42])	2 trials, n=1081	Low

Function	Donepezil (up to 10 mg/day)	Severe	Mean ADCS-ADL change, SMD, 0.18 [95% CI, 0.03 to 0.32]	3 trials, n=733	Low
	Rivastigmine (12 mg/day orally or 9.5 mg/day patch)	Mild to moderate	-ADCS-ADL change (SMD, 0.21 [95% CI, 0.09 to 0.33] -Mean DAD change (SMD, 0.19 [95% CI, 0.03 to 0.37])	1 trial, n=782 1 trial, n=536	Low
Clinical Impression of Change	Donepezil	Mild to moderate	Likelihood improved: 28% vs. 16% (up to 10 mg/d); ARD, 12% [95% CI, 8% to 16%]; NNTB, 8 [95% CI, 6 to 13]; RR, 1.89 [95% CI, 1.46 to 2.45]	4 trials, n=1585	Moderate
		Severe/ moderate to severe	Likelihood improved: 38% vs. 28% (up to 10 mg/d); ARD, 10% [95% CI, 5% to 15%]; NNTB, 10 [95% CI, 7 to 20]; RR, 1.34 [95% CI, 1.13 to 1.58]	5 RCT, n=1398	Low
	Rivastigmine (12 mg/day orally or 9.5 mg/day patch)	Mild to moderate	Likelihood improved: favors rivastigmine (31% vs. 21%; ARD, 10% [95% CI, 7% to 14%]; NNTB, 10 [95% CI, 7 to 14]; RR, 1.47 [95% CI, 1.20 to 1.80]	4 trials, n=2,201	Moderate
		Moderate to severe	Likelihood improved: favors rivastigmine (22% vs. 9%; ARD, 13% [95% CI, 3 to 22]; NNTB, 8 [95% CI, 5 to 33]; RR, 2.34 [95% CI, 1.17 to 4.68]	1 trial, n=210	Low
	Memantine without ACHEI	Mild to moderate	Likelihood unchanged/improved: Favors memantine (67% vs. 51%; ARD, 17% [95% CI, 7% to 26%]; NNTB, 6 [95% CI, 4 to 14]; RR, 1.33 [95% CI, 1.12 to 1.57]) Mean CIBIC-Plus change: Favors memantine: SMD, -0.27 [95% CI, -0.49 to -0.05])	1 trial, n=403	Low
	Memantine with ACHEI	Moderate to Severe	Mean CIBIC-Plus change favors add-on memantine: SMD, -0.25 [95% CI, -0.37 to -0.12	2 trials, n=1081	Low
SAEs	Donepezil	Mild to moderate	Increased risk 10.7% vs. 8.7% (up to 10 mg/d); ARD, 2% [95% CI, -0.3 to 4.3]; NNTH, 50 [95% CI, NNTH 23; NNTB 333]; RR, 1.32 [95% CI, 1.03 to 1.68]	8 trials, n=2521	Low
Withdrawals due to AEs	Donepezil	Severe/ moderate to severe	Increased risk 12.6% vs. 8.1% (up to 10 mg/d); ARD, 4.5% [95% CI, 1.5 to 7.6]; NNTH, 23 [95% CI, 14 to 67]; RR, 1.54 [95% CI, 1.13 to 2.10]	5 trials, n=1559	Low
	Galantamine	Mild to moderate	Increased risk: 18% vs 8.8%; ARD, 9.2% [95% CI, 4 to 14.4]; NNTH, 11 [95% CI, 7 to 25]; RR, 2.04 [95% CI, 1.27 to 3.28]	1 trial, n=407	Low
Abbreviations	ACHEIs=Acetylcholinesterase Inhibitors; AD=Alzheimer's-type dementia; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognition; ADCS-ADL=Alzheimer's Disease Cooperative Study—Activities of Daily Living; AEs=adverse events; ARD = absolute risk difference; CI = confidence interval; Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus); MMSE=Mini-Mental State Examination;				

	NNTB=number needed to benefit; NNTH=number needed to harm; PDS=Progressive Deterioration Scale; RR = relative risk; SAEs=Serious Adverse Events; SIB=severe impairment battery; SMD=standard mean difference

For most comparisons and outcomes between prescription drugs and other active treatments, strength of evidence was graded as insufficient.[1] Due to inconsistent data, authors were unable to formulate conclusions of comparative differences between select prescription drugs (galantamine, donepezil, and memantine) in cognitive tests, QoL, function, serious adverse events (SAEs), or withdrawals due to adverse events. In addition, there was insufficient evidence to draw conclusions about differences between memantine and other antipsychotics for agitation, general behavior, or SAEs. No variations in outcomes by participants or drug characteristics were observed.

Evidence was limited by high risk of bias for many included studies, small sample sizes, short follow-up time, and lack of reporting of withdrawals due to harms (somnolence, confusion, falls or extrapyramidal symptoms).[1] There was a potential for publication bias since many eligible trials with high risk-of-bias and attrition were excluded from analysis. Many trials used imputation methods for missing data which may have led to an overestimation of treatment benefit. [1]

Cochrane

A 2019 Cochrane Collaboration systematic review evaluated the clinical efficacy and safety of memantine for patients with dementia.[24] A total of 44 randomized, double-blind trials of 12 weeks or more were included in the review (n=9811), most of which were conducted in patients with Alzheimer's-type dementia (29 trials; n=7885).[24] Trials involved comparisons of the effects of memantine therapy versus placebo on cognitive function, behavior and mood, activities of daily living, and clinical global rating based on 24- to 30-week data.[24] The overall risk of bias for the majority of studies was either unclear or low. In moderate to severe Alzheimer's Dementia with or without concomitant ACHEIs, there was high-certainty evidence that showed a modest clinical benefit for memantine 20 mg (or equivalent) versus placebo in clinical global rating score (SMD -0.21; 95% CI -0.14 to -0.30; I^2=0%; 10 studies, n=2797); cognitive function (SMD -0.27; 95% CI -0.34 to -0.21; I^2=30%; 13 studies, n=3337); decline in activities of daily living (SMD -0.16; 95% CI -0.24 to -0.09; I2=0%; 11 studies, n=2687); and behavior and mood (SMD -0.14; 95% CI -0.21 to -0.08; I^2=8%; 14 studies, n=3674).[24] There was moderate certainty evidence that memantine is more likely than placebo to result in dizziness (RR 1.59, 95% CI 1.28 to 1.98).[24]

Agency for Healthcare Research and Quality

A 2017 AHRQ report evaluated interventions to prevent age-related cognitive decline, mild cognitive impairment, and clinical Alzheimer's-type dementia.[25] Of 10 eligible studies, all but one was assessed as high risk of bias and were not analyzed.[25] One study (n=769) with low-to-medium risk of bias assessed donepezil compared to placebo for cognitive benefit. At 3 years, there was low-quality evidence of no statistically significant difference between donepezil and placebo in delayed progression from mild cognitive impairment (MCI) to AD, improvements in neuropsychological performance, processing speed, or memory.[25] Evidence was limited by inconsistencies in the outcome definitions, small sample sizes, limited follow-up, and attrition.[25] Overall, the high risk of study bias, wide variety of measurement tools, and lack of head to head studies significantly limited the ability to formulate conclusions of comparative benefits or harms between interventions for persons with MCI or AD.[25]

After review, 11 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:

High Quality Guidelines:

National Institute for Health and Care Excellence (NICE)[26]

Since the previous AD class review, NICE updated guidelines in 2018 for assessment, management, and support for people living with Alzheimer's dementia and their caregivers.[26]

Initial pharmacological management of Alzheimer's disease[26]

- Acetylcholinesterase (AChE) inhibitors donepezil, galantamine and rivastigmine as monotherapies are recommended for managing mild to moderate AD
- Start with the most cost-effective agent or switch to alternate based on adherence, comorbidity, drug interactions, etc.
- Memantine monotherapy is recommended for managing moderate AD for people who are intolerant of or have a contraindication to AChE inhibitors or severe AD

Continuation of therapy for AD[26]

For people with a diagnosis of AD who are already taking an AChE inhibitor:

- Consider memantine in addition to an AChE inhibitor if they have moderate disease.
- Offer memantine in addition to an AChE inhibitor if they have severe disease.
- Primary care prescribers may start treatment with memantine without consultation from a specialist clinician.

Therapy Discontinuation for AD[26]

- Do not stop AChE inhibitors in people with AD because of disease severity alone.

US Preventive Services Task Force (USPSTF)[27]

The USPSTF updated their 2014 review of screening for cognitive impairment, ranging from mild cognitive impairment to mild ro moderate dementia, in community-dwelling adults aged 65 years or older. The USPSTF found that the current evidence is insufficient to assess the balance of benefits and harms of screening for cognitive impairment in this population.[27]

Additional Guidelines for Clinical Context:

The Journal of Prevention of Alzheimer's Disease recently published guidelines for appropriate use of aducanumab, a new monoclonal antibody approved for the treatment of mild AD.[28] The document was written by 2 authors based on guidance from an undisclosed expert panel.[28] There was no systematic guideline development method described, strength of evidence for guideline recommendations were not provided, and the recommendations were based on expert opinion.[28] In addition, the authors reported several conflicts of interests including providing consultative services to aducanumab manufacturer Biogen as well as receiving research support and consultancy fees.[28] One author reported serving as co-chair of the investigator steering committee for the ENGAGE trial.[28] Based these factors, the recommendations from this publication were excluded from this review.

New Formulations: None identified.

New FDA Safety Alerts: None identified.

Randomized Controlled Trials:
A total of 143 citations were manually reviewed from the initial literature search. None of the identified studies met quality inclusion criteria. All RCT citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). Key inclusion criteria for RCTs are listed in **Appendix 4**. The phase 3 RCTs evaluating efficacy of aducanumab were included in the new drug evaluation below as they were the primary trials used for FDA-approval.

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:
Aducanumab (Aduhelm™) is a recombinant monoclonal antibody that targets aggregated beta amyloid protein in brain tissue.[2] The presence of brain amyloid is a hallmark feature of Alzheimer's disease.[2,8] The exact relationship between brain amyloid and the development and progression of AD clinical syptoms is not completely understood.[2,3,8] Although beta amyloid has been suspected to cause acute neuronal toxicity and neurodegeneration in AD pathogenesis, the removal of amyloid plaque to slow AD progression has not been proven.[2,3,8] Treatment with aducanumab demonstrated a dose- and duration-dependent clearance of beta amyloid plaque from the brain.[2] In June 2021, aducanumab received FDA approval under the accelerated pathway for the treatment of AD based on a surrogate endpoint of amyloid plaque reduction as measured by PET imaging.[2,4] Continued approval will require verification of actual clinical benefit in subsequent trials.[2,4]

The safety and efficacy of aducanumab in patients with early stage AD dementia were evaluated in 2 identically designed, multicenter, randomized, double-blind, placebo-controlled, parallel-group, unpublished phase 3 trials: Study 302 ("EMERGE") (N=1638) and Study 301 ("ENGAGE") (N=1647).[2,4] The primary outcome was change from baseline in the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score compared to placebo at week 78.[2,4] Secondary outcomes assessed the clinical progression of AD as measured by Mini-Mental State Examination (MMSE), AD Assessment Scale-Cognitive Subscale (ADAS-Cog 13), and AD Cooperative Study-Activities of Daily Living Inventory (ADCS-ADL-MCI).[2,4] A pre-specified futility threshold was set to assess if the trials were unlikely to meet their primary endpoint upon completion.[2]

Both studies enrolled patients with confirmed presence of amyloid pathology via Positron Emission Tomography (PET) scan confirmation and Stage 3 (mild cognitive impairment) or Stage 4 (mild dementia) AD.[2,29] Of those screened, 16% failed entry due to a negative amyloid PET scan.[2] At baseline, both studies required a CDR-SB score of 0.5 and MMSE score of 24-30.[2] Excluded from the studies were patients with a history of bleeding disorders or on anticoagulant therapy.[2] Patients were randomized 1:1:1 to receive low dose aducanumab (3 or 6 mg/kg), high dose aducanumab (10 mg/kg), or placebo every 4 weeks for 18 months.[2] Randomization was stratified by site and by ApoE ε4 carrier status (carrier or non-carrier).[2] A titration period of up to 6 months was employed until target dose was achieved.[2] Mean age at baseline was 71 years (range 50-85 years).[2] ARIA severity was evaluated and categorized through an unvalidated severity scale (see **Table 3**).

Table 3. ARIA MRI Classification Criteria[4]

ARIA Type	Radiographic Severity		
	Mild	**Moderate**	**Severe**
ARIA-E	FLAIR hyperintensity confined to sulcus and or cortex/subcortical white involvement, each matter in one location <5 cm	FLAIR hyperintensity 5 to 10 cm, or more than 1 site of measuring <10 cm	FLAIR hyperintensity measuring >10 cm, often with significant subcortical white matter and/or sulcal involvement. One or more separate sites of involvement may be noted.
ARIA-H microhemorrhage	≤4 new incident microhemorrhages	5 to 9 new incident microhemorrhages	10 or more new incident microhemorrhages
ARIA-H superficial siderosis	1 focal area of superficial siderosis	2 focal areas of superficial siderosis	>2 focal areas of superficial siderosis
Abbreviations: ARIA-E=amyloid-related imaging abnormalities edema; ARIA-H=amyloid-related imaging abnormalities hemorrhage; FLAIR= Fluid attenuated inversion recovery			

An interim futility analysis was planned after 50% of the patients enrolled in studies 301 and 302 had the opportunity to complete the week 78 visit. In December 2018 interim data collected from the analysis revealed CDR-SB scores had continued to decline in both aducanumab treatment and placebo groups.[2,3] Both trials were discontinued in March 2019 based on the findings.[2,3] However, after post-hoc analysis of additional missing patient data, it was reported the high-dose aducanumab arm from study 302 had experienced less CDR-SB score decline compared to placebo after 78 weeks.[3] The statistically significant result (p=0.01) from the high-dose group from study 302 was not consistent with the high-dose group in study 301 (p=0.83).[3] Nonetheless, a new application with the supplementary data was subsequently submitted to the FDA.[3]

Upon reanalysis of study 302 data, the low-dose aducanumab group showed no statistically significant difference in CDR-SB score reduction or any significant improvements in secondary outcome measures compared to placebo at week 78.[3] However, in the high-dose group there was a statistically significant change from baseline in CDR-SB score compared to placebo (-0.39 points; p=0.0120).[2,3] The high dose group also reported statistically significant changes in the secondary endpoints of MMSE scores (0.6; p=0.0493), ADAS-Cog 13 score (-1.4; p=0.0097), and ADCS-ADL-MCI score (1.7; p=0.0006) compared to placebo.[2] Although no minimal clinically important differences were prespecified, it is unlikely that less than 1-point difference in the CDR-SB or MMSE, or relatively small magnitude of benefit observed in the other secondary endpoints, were clinically significant.[2,3,17-21]

In study 301 reanalysis, there were no statistically significant differences observed in any primary or secondary endpoints for either the low-dose or high-dose aducanumab groups compared to placebo at 78 weeks.[3] In contrast to study 302, the high dose aducanumab groups reported numerically inferior results compared to placebo.[3] There was no evidence to suggest any differences in baseline characteristics or randomization inconsistencies among the participants in study 301 versus study 302.[2,3]

The FDA limited the labeled indication for aducanumab to patients with mild AD.[2-4] The accelerated approval process requires a phase 4 confirmatory clinical trial for clinical safety and efficacy and the manufacturer has until August 2022 to finalize the trial design and until August 2029 to complete the study.[30]

Aducanumab was approved based on a surrogate outcome of brain amyloid reduction along with positive statistical findings obtained from post-hoc data in a high-dose treatment group in one clinical trial.[2,4] Risk of bias could not be formally assessed. Efficacy data for the high-dose aducanumab patients (those with at least 10 uninterrupted administrations) were based on known treatment compliance, so it is unclear if the post-hoc analysis may have introduced selection bias and overestimated an already modest treatment effect.[3] Study 302 and study 301 results were largely contradictory, therefore the inconsistency in results between two identically designed trials decreases confidence that the statistically significant findings of Study 302 represent a true effect.[3] Combining the results from the two trials found no statistically significant clinical benefit for high-dose aducanumab.[3] In the FDA statistical review, it was noted that there were multiple subgroup analyses, but none of them were at the sample size planned in the protocol which made interpretation of p-value significance problematic.[3] The effects of attrition and missing data were unable to be assessed. With a large amount of missing data in the final ITT population (>45% per group) and lower rate missing in the "Opportunity to Complete" group dataset, there may have been group imbalances that favored the high-dose group.[3] There has been no conclusive evidence to support the claim that changes in beta-amyloid plaque levels lead to clinically meaningful improvements in AD symptoms or a slowing of cognitive or functional decline.[3,22] The uncertain benefits of aducanumab are currently applicable to those with mild symptoms and positive brain amyloid PET imaging.[2] Efficacy is unknown for those diagnosed with moderate to severe AD or who have a negative PET scan, preexisting cardiovascular disease, psychiatric disease, neurologic disease, renal or liver impairment. [2-4] The studies enrolled a low proportion of patients who were black or African American (~1%), Hispanic or Latino (~4%), American Indian or Alaska Native (<1%) which limits applicability of study results to these populations.[2] Aducanumab studies have failed to produce evidence of consistent clinical benefits for cognitive or functional outcomes in mild AD and long-term efficacy data beyond 78 weeks is unknown.

Clinical Safety:

Adverse events that occurred in at least 10% of the patients treated with aducanumab were ARIA-E and ARIA-H which included microhemorrhage and superficial siderosis, headache (including related terms such as head discomfort, migraine, migraine with aura, and occipital neuralgia), and increased falls.[2-4] In Studies 301 and 302, ARIA (-E and/or -H) was observed in 41% of patients treated with aducanumab with a planned dose of 10 mg/kg (454 out of 1105), compared to 10% of patients on placebo (111 out of 1087).[2-4] The incidence of ARIA-E was higher in ApoE ε4 carriers than in ApoE ε4 non-carriers (42% and 20%, respectively).[2-4] The long-term effects of vascular compromise caused by ARIA-E and ARIA-H on Alzheimer disease progression or prognosis is unclear. Serious adverse events were reported in 0.3% of patients treated with aducanumab and hypersensitivity reactions including angioedema and urticaria were reported in one patient.[2-4]

For both Studies 301 and 302, the aducanumab high-dose group had the highest percentage of discontinuations and withdrawals compared to the aducanumab low-dose and placebo groups (see **Table 4**).

Table 4. Combined Patient Disposition for Studies 301 and 302[3]

Studies 301 and 302 (Combined Patient Disposition)	**High-dose Aducanumab** (n=1102)	**Low-dose Aducanumab** (n=1090)	**Placebo** (n=1093)
Discontinued Treatment	279/1102 (25%)	213/1090 (20%)	178/1093 (16%)
Withdrew from Study	144/1102 (13%)	114/1090 (10%)	97/1093 (9%)
Total Discontinuations and Withdrawals from Studies	423/1102 (38%)	327/1090 (30%)	275/1093 (25%)

A summary of reported adverse reactions observed with aducanumab use is presented in **Table 5**. Patients were excluded from the aducanumab studies if they were on an antiplatelet or anticoagulation medication other than aspirin 325 mg daily or less, or if they had a history of bleeding disorder, blood clotting disorder, abnormal coagulation profile, hypertension, prior cortical or lacunar infarct, or seizure within 10 years of screening.[2-4] Therefore, there are unkown harms for patients with pre-existing risk factors for bleeding, including concomitant medications that could increase the risk for bleeding, if treated with aducanumab.[2-4] There are no adequate data on aducanumab use in pregnant or lactating women to evaluate for drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.[2,4]

Table 5. Adverse Reactions Observed in AD Patients Treated with Aducanumab 10 mg/kg versus Placebo [2-4]

Adverse Reactions	**Aducanumab** N=1105 %	**Placebo** N=1087 %
ARIA-E	35	3
Headache	21	16
ARIA-H microhemorrhage	19	7
ARIA-H superficial siderosis	15	2
Fall	15	12
Diarrhea	9	7
Confusion/Delirium/Altered Mental Status/Disorientation	8	4

Look-alike / Sound-alike Error Risk Potential: adalimumab (Humira™)

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Mortality
2) Cognitive Function
3) Quality of Life
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) Clinical Dementia Rating-Sum of Boxes (CDR-SB) score

Table 6. Pharmacology and Pharmacokinetic Properties.[4]

Parameter	
Mechanism of Action	Human, immunoglobulin gamma 1 (IgG1) monoclonal antibody which reduces aggregated soluble and insoluble amyloid beta plaques in patients with Alzheimer's disease
Oral Bioavailability	N/A
Distribution and Protein Binding	Volume of Distribution: 9.63 L; Protein Binding not reported
Elimination Half Life	24.8 days
Metabolism/Excretion	Degraded into small peptides and amino acids via catabolic pathways

Abbreviations: L = liters; N/A = Not Applicable

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
donepezil HCl	ARICEPT	TABLET	ORAL	Y
donepezil HCl	DONEPEZIL HCL	TABLET	ORAL	Y
galantamine HBr	GALANTAMINE ER	CAP24H PEL	ORAL	Y
galantamine HBr	RAZADYNE ER	CAP24H PEL	ORAL	Y
galantamine HBr	GALANTAMINE HBR	TABLET	ORAL	Y
memantine HCl	MEMANTINE HCL	SOLUTION	ORAL	Y
memantine HCl	MEMANTINE HCL	TAB DS PK	ORAL	Y
memantine HCl	NAMENDA	TAB DS PK	ORAL	Y
memantine HCl	MEMANTINE HCL	TABLET	ORAL	Y
memantine HCl	NAMENDA	TABLET	ORAL	Y
rivastigmine	EXELON	PATCH TD24	TRANSDERM	Y
rivastigmine	RIVASTIGMINE	PATCH TD24	TRANSDERM	Y
donepezil HCl	DONEPEZIL HCL ODT	TAB RAPDIS	ORAL	N
galantamine HBr	GALANTAMINE HYDROBROMIDE	SOLUTION	ORAL	N
memantine HCl	MEMANTINE HCL ER	CAP SPR 24	ORAL	N
memantine HCl	NAMENDA XR	CAP SPR 24	ORAL	N
memantine HCl	NAMENDA XR	CAP24 DSPK	ORAL	N
memantine HCl/donepezil HCl	NAMZARIC	CAP SPR 24	ORAL	N
memantine HCl/donepezil HCl	NAMZARIC	CAP24 DSPK	ORAL	N
rivastigmine tartrate	RIVASTIGMINE	CAPSULE	ORAL	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to July 22, 2021

1 *donepezil.mp. or Donepezil/ 4330*
2 *galantamine.mp. or Galantamine/ 2362*
3 *rivastigmine.mp. or Rivastigmine/ 2035*
4 *memantine.mp. or Memantine/ 4023*
5 *aducanumab.mp./ 122*
6 *Alzheimer Disease/ or alzheimers.mp./ 165215*
7 *1 or 2 or 3 or 4 or 5/ 10411*
8 *6 and 7 / 5362*
9 *limit 8 to (english language and humans and yr="2016 -Current" and (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or consensus development conference or controlled clinical trial or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review"))/ 143*

Appendix 3: Prescribing Information Highlights

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

ADUHELM™ (aducanumab-avwa) injection, for intravenous use
Initial U.S. Approval: 2021

RECENT MAJOR CHANGES

Indications and Usage (1) 7/2021

INDICATIONS AND USAGE

ADUHELM is an amyloid beta-directed antibody indicated for the treatment of Alzheimer's disease. Treatment with ADUHELM should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with ADUHELM. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s). (1)

DOSAGE AND ADMINISTRATION

- Titration is required for treatment initiation. (2.1)
- The recommended maintenance dosage is 10 mg/kg administered as an intravenous infusion over approximately one hour every four weeks. (2.1)
- Obtain a recent (within one year) brain MRI prior to initiating treatment. (2.2, 5.1)
- Obtain MRIs prior to the 7th and 12th infusions. If radiographic severe ARIA-H is observed, treatment may be continued with caution only after a clinical evaluation and a follow-up MRI demonstrates radiographic stabilization (i.e., no increase in size or number of ARIA-H). (2.2, 5.1)
- Dilution in 100 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 0.2 or 0.22 micron in-line filter. (2.5)

DOSAGE FORMS AND STRENGTHS

Injection:

- 170 mg/1.7 mL (100 mg/mL) solution in a single-dose vial (3)
- 300 mg/3 mL (100 mg/mL) solution in a single-dose vial (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Amyloid Related Imaging Abnormalities (ARIA): Enhanced clinical vigilance for ARIA is recommended during the first 8 doses of treatment with ADUHELM, particularly during titration. If a patient experiences symptoms which could be suggestive of ARIA, clinical evaluation should be performed, including MRI testing if indicated. (2.2, 5.1)
- Hypersensitivity Reactions: Angioedema and urticaria have occurred. If a hypersensitivity reaction occurs, promptly discontinue the infusion of ADUHELM and initiate appropriate therapy. (5.2)

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact Biogen at 1-833-425-9360 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 7/2021

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

Appendix 5. Proposed Prior Authorization Criteria

Aducanumab

Goal(s):

- To support medically appropriate 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 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. Aducanumab Dosing and ARIA Monitoring

IV Infusion (every 4 weeks)	Dose	ARIA Monitoring
Infusion 1 and 2	1 mg/kg	MRI 90 days prior to Infusion 1
Infusion 3 and 4	3 mg/kg	MRI 28 days prior to Infusion 7
Infusion 5 and 6	6 mg/kg	
Infusion 7 to 11	10 mg/kg	MRI 28 days prior to Infusion 12
After Infusion 12	10 mg/kg	MRI annually

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this being 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

Approval Criteria		
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #5
5. Is the request for continuation of therapy in a patient previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #6
6. Is the therapy prescribed by or in consultation with a neurologist?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. 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 (CDR)-Global Score of 0.5; **AND** • Objective evidence of cognitive impairment at screening; **AND** • Mini-Mental Status Exam (MMSE) score between 24 and 30 (inclusive); **AND** • Positron Emission Tomography (PET) scan positive for amyloid beta plaque or presence of amyloid confirmed in cerebrospinal fluid (CSF)?	**Yes:** Go to #8 Document test results.	**No:** Pass to RPh. Deny; medical appropriateness There is insufficient evidence for use of this agent in treating moderate or severe AD

Approval Criteria		
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 assessed and documented baseline disease severity within the last 6 months utilizing an objective measure/tool (e.g., MMSE, Alzheimer's Disease Assessment Scale-Cognitive Subscale [ADAS-Cog-13], 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], or other validated AD patient monitoring tool)?	**Yes:** Record baseline measurement. Go to #10	**No:** Pass to RPh. Deny; medical appropriateness
10. 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**]-hemosiderin deposition (brain bleeding or protein deposits on brain/spinal cord)?	**Yes:** Record scheduled appointment dates: _____ Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. Has the prescriber ruled out the presence of any vascular abnormalities which may increase bleeding risk/ARIA **AND** has the patient been screened to ensure they are not currently receiving anticoagulant or antiplatelet therapy (excluding aspirin 81 mg)?	**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 (CDR)-Global Score of 0.5; AND • Objective evidence of cognitive impairment at screening; AND • Mini-Mental Status Exam (MMSE) score between 24 and 30 (inclusive)	**Yes:** Go to #2	**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. Is there documented evidence of beta-amyloid reduction compared to baseline confirmed by post-infusion brain imaging or CSF testing?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Was there an adverse event (ARIA-H or ARIA-E [brain microhemorrhage, superficial siderosis, or edema], hypersensitivity reaction, etc.) observed or reported with aducanumab therapy?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #5
5. Has the patient received at least 6 months of uninterrupted aducanumab therapy?	**Yes:** Go to #6	**No:** Approve remaining duration of the 6-month titration period

Renewal Criteria		
6. Is there documentation that, compared to baseline assessment, aducanumab therapy has resulted in: • cognitive or functional improvement **OR** • disease stabilization **OR** • reduction in clinical decline compared to the natural disease progression? The same clinical measure used to assess AD (e.g., CDR-SB, MMSE, ADAS-Cog-13, 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: 10/21 (DE)
Implementation: 1//1/22