Pharmacy Management Drug Policy

SUBJECT: Anti-Amyloid Directed Therapies **POLICY NUMBER: PHARMACY-100** **EFFECTIVE DATE: 06/24/2021** **LAST REVIEW DATE: 09/07/2023**	

If the member's subscriber contract excludes coverage for a specific service or prescription drug, it is not covered under that contract. In such cases, medical or drug policy criteria are not applied. This drug policy applies to the following line/s of business:

Policy Application

Category:	☒ Commercial Group (e.g., EPO, HMO, POS, PPO)	☒ Medicare Advantage
	☒ On Exchange Qualified Health Plans (QHP)	☐ Medicare Part D
	☒ Off Exchange Direct Pay	☒ Essential Plan (EP)
	☒ Medicaid & Health and Recovery Plans (MMC/HARP)	☐ Child Health Plus (CHP)
	☐ Federal Employee Program (FEP)	☐ Ancillary Services
	☒ Dual Eligible Special Needs Plan (D-SNP)	

DESCRIPTION:

Alzheimer's disease (AD) is a progressive brain disease characterized by decline in memory, thinking, and physical function. It is estimated that AD affects 6.2 million Americans 65 years of age and older and is the sixth leading cause of death in the United States.[1] Alzheimer's disease progresses on a continuum categorized by three phases: (1) preclinical AD (2) mild cognitive impairment (MCI) due to AD and (3) Alzheimer's dementia which is further classified into mild, moderate, and severe. As the disease progresses, noticeable symptom changes occur in memory, thinking, and behavioral, impacting the patient's ability to perform activities of daily living. Risk factors for late-onset AD include older age, mutations in the apolipoprotein e4 gene (APOE-e4), and family history of AD. Early-onset AD has been linked to several less common genetic mutations.[1] No single test is used to diagnose Alzheimer's dementia but rather a variety of assessments, cognitive tests, and biomarkers collectively assist in making the diagnosis.[2]

While the exact mechanism of the disease is not fully understood, several hypotheses exist that focus on different features of the disease including, but not limited to, accumulation of beta-amyloid proteins, abnormal formation of a protein called tau, inflammation, and cholinergic abnormalities.[3] Current and prospective drug targets aim at correcting these imbalances with recent focus on the accumulation of beta-amyloid plaques and neurofibrillary tangles of phosphorylated tau protein. It is believed that the accumulation of these plaques and tangles contribute to damage and death of neurons in the brain.[4,5]

Pharmacological treatments for Alzheimer's dementia include cholinesterase inhibitors (i.e., donepezil, rivastigmine, and galantamine) used primarily for early and intermediate AD and memantine, a glutamate antagonist, indicated for moderate to severe AD. These treatments have not been shown to stop or slow the disease progression but are used to treat cognitive and functional symptoms of the disease.[1]

The FDA announced on June 7th, 2021, the approval of Aduhelm (aducanumab-avwa), the first monoclonal antibody directed against amyloid-beta. On January 6th, 2023, the FDA approved the second anti-amyloid beta monoclonal antibody called Leqembi (lecanemab-irmb). Both drugs were studied in patients with Alzheimer's Disease with mild cognitive impairment or mild dementia and received accelerated approval based on reduction in amyloid beta plaques. There are no safety or

effectiveness data on initiating these treatments at earlier or later stages of the disease than were studied. Phase III trials are underway for other anti-amyloid beta directed monoclonal antibodies, primarily in early stages of AD.

Additionally, other amyloid beta drug targets include beta-site amyloid precursor protein cleaving enzymes (BACEs), y-secretases, and inhibitors of beta-amyloid deposition (anti-aggregation compounds). While several clinical trials for these amyloid targeted therapies have demonstrated the intended mechanistic effects on beta-amyloid, this has yet to be translated into a clinical benefit. Limitations of these trials have been recognized, including the fact that many were studied in later stages of AD.[5]

ADUHELM (aducanumab-avwa)

Aduhelm (aducanumab-avwa) is an amyloid beta-directed antibody indicated for treatment of Alzheimer's disease. In July 2021, updates were made to the Aduhelm prescribing information to clarify that treatment should be initiated in patients with MCI or mild dementia stage of disease, the same as the population studied in clinical trials. The label further states there is no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied.[6] The FDA approved Aduhelm (aducanumab-avwa) using the accelerated approval pathway, which allows for earlier approval of drugs to treat serious or life-threatening conditions based on a surrogate endpoint that is reasonably likely to predict a clinical benefit, but is not itself a measure of clinical benefit.[7,8] The surrogate endpoint used for this accelerated approval was reduction of amyloid beta plaque in the brain. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.

The efficacy of Aduhelm (aducanumab-avwa) was evaluated in two double-blind, randomized, placebo-controlled parallel group Phase 3 studies (ENGAGE and EMERGE) and a Phase 1b trial (PRIME). Details from the ENGAGE and EMERGE trials are discussed below.[9,10]

ENGAGE and EMERGE TRIALS

Methods

For the Phase 3 trials (ENGAGE and EMERGE), patients 50-85 years of age were eligible to participate if they met criteria for MCI due to AD or mild AD dementia and had confirmed evidence of beta-amyloid by positron emission tomography (PET). Patients also had to meet the following criteria: Clinical Dementia Rating (CDR) global score of 0.5, Repeatable Battery for Assessment of Neuropsychological Status (RBANS) delayed memory index score $\leq$ 85, and Mini-Mental State Examination (MMSE) score of 24-30.

Patients in the ENGAGE trial and EMERGE trials were randomized in a 1:1:1 ratio to receive low-dose aducanumab (3 or 6 mg/kg given intravenously (IV) for APOE-e4 carriers and noncarriers, respectively), high-dose aducanumab (10 mg/kg given IV), or placebo every 4 weeks for 18 months. This was followed by an optional, dose-blind, long term extension period. An initial titration period of up to 6 months occurred for both trials to the maximum target dose. Of note, initially APOE-e4 carriers were titrated to a maximum of 6 mg/kg in the high dose group, but this protocol was later adjusted to 10 mg/kg.

The primary endpoint was change from baseline in Clinical Dementia Rating-Sum of Boxes (CDR-SB) score at 18 months. The CDR-SB score assess cognition and function where a higher score indicates greater disease severity. Secondary endpoints assessed clinical decline measure by the Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale – Cognitive 13-Item

Scale (ADAS-Cog 13), and Alzheimer's Disease Cooperative Study – Activities of Daily Living – Mild Cognitive Impairment (ADCS-ADL-MCI). Additionally, both trials included various biomarker sub-studies to assess brain amyloid by positron emission tomography (PET), beta-amyloid levels in the cerebrospinal fluid (CSF), intracellular tau accumulation in the CSF measured by phosphorylated tau (p-tau), neurodegeneration measured by CSF total Tau (t-Tau) and tau pathophysiology assessed by Tau PET.

Futility Analysis

An interim analysis for futility was prespecified in the study protocols to allow for early termination of the study if the drug was found to be ineffective in an effort to limit exposure to the placebo and drug. The results of the prespecified futility analysis showed futility and the ENGAGE and EMERGE trials were terminated prior to planned completion. After review of the futility analysis, it was determined that the two studies had differing results and to better understand this divergence the manufacturer conducted additional analysis with a larger dataset. The manufacturer in conjunction with the FDA determined that the use of this larger dataset was "interpretable and suitable for additional consideration".[9] The results using this larger dataset are outlined below.

Results

For the ENGAGE trial, neither treatment group had a statistically significant difference from placebo on the primary or secondary efficacy endpoints. Of the 1,647 patients in the ENGAGE study, 585 patients were enrolled in the amyloid PET subgroup with 347 evaluated at week 78. In the amyloid PET sub-study, compared to placebo, there was a statistically significant time and dose-dependent reduction in brain amyloid plaque measured by PET for both treatment groups. CSF levels of p-Tau and t-Tau were not significantly different from placebo.

Conversely, the EMERGE trial (N=1,638) showed a statistically significant improvement in the high-dose arm versus placebo in the primary outcome measure, CDR-SB (22% less decline, p=0.0120) and a numerical, though not statistically significant, improvement in the low-dose arm. Secondary endpoints related to MMSE, ADAS-Cog13 and ADCS-ADL-MCI were statistically improved compared to placebo in the high dose group. In the amyloid PET sub-study (N=488) a time and dose-dependent reduction in brain amyloid plaque was statistically significant in the treatment groups versus placebo. Similarly, CSF p-Tau and CSF t-Tau were statistically significantly reduced in the treatment group versus placebo (N=78).

The investigators concluded that the two trials were partially discordant. The low dose groups of both studies showed similar trends across clinical and biomarker measurements, but the high dose arms diverged on their respective endpoints. Investigators determined through a post-hoc exploratory analysis that two main factors may explain this difference. The first being patients in the ENGAGE study had lower exposure to the 10 mg/kg dosing which was an important factor for efficacy. Additionally, the investigators determined an imbalance in the number and distribution of rapid progressing Alzheimer's disease patients in the high-dose group of the ENGAGE trial.[9] As previously noted, this was an exploratory post-hoc analysis which carries inherent limitations and therefore these results must be interpreted cautiously.

Aduhelm Safety

Combined safety data from the ENGAGE and EMERGE trial reported 90.7% of patients treated with aducanumab experienced an adverse effect compared to 86.9% in the placebo group. Adverse events with ≥5% incidence in the aducanumab 10 mg/kg group that exceeded the incidence in the

placebo group by ≥2% includes: amyloid-related imaging abnormalities-edema (ARIA-E), headache, amyloid-related imaging abnormalities– hemorrhage or superficial siderosis (ARIA-H), fall, and diarrhea.

ARIA is associated with amyloid-modifying therapies and is seen on brain MRI. The MRI findings can include edema or effusion (ARIA-E) or brain microhemorrhage or localized superficial siderosis (ARIA-H).

FDA Advisory Committee Review

On November 6, 2020, the FDA Peripheral and Central Nervous System Drugs Advisory Committee convened to review the application for aducanumab for the treatment of Alzheimer's disease and vote on several questions posed to the Committee.[11]

When was asked if the EMERGE trial, independent of the ENGAGE trial, provides "strong evidence that supports the effectiveness of aducanumab for the treatment of Alzheimer's disease" the Committee voted: 1 yes, 8 no, and 2 uncertain. Additionally, the Committee was somewhat split on whether the manufacturer presented strong evidence of a pharmacodynamic effect on Alzheimer's disease pathophysiology with 5 members voting yes and 6 uncertain.

Almost all Committee members agreed (10 no, 1 uncertain) that it was not reasonable to consider the EMERGE study as primary evidence of effectiveness of aducanumab for the treatment of Alzheimer's disease. Members expressed reluctancy to suggest approval for aducanumab for the treatment of Alzheimer's disease because of insubstantial evidence. The individual who was uncertain did highlight that the EMERGE trial was positive, and the PRIME study provided some additional evidence.

The Institute for Clinical and Economic Review (ICER)

ICER is a non-profit research organization that evaluates clinical and economic evidence for the value of prescription drugs, medical tests, devices, and health system innovations. ICER compiled an evidence report of aducanumab from both a clinical and economic perspective.[12] In a statement released on June 7, 2021, following the FDA-approval of Aduhelm (aducanumab), ICER stated:

"Our review of the evidence was concordant with that of many independent experts: **current evidence is insufficient to demonstrate that aducanumab benefits patients**. The avenue forward has seemed clear: another study would be needed to reduce the substantial uncertainty about the drug's effectiveness, a requirement of even greater priority because of the drug's common and potentially serious side effects."[13]

LEQEMBI (lecanemab-irmb)

Leqembi (lecanemab-irmb) is the second amyloid beta-directed antibody indicated for the treatment of Alzheimer's disease and should only be initiated in patients with mild cognitive impairment or mild dementia stage of disease. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied.
The efficacy of Leqembi (lecanemab-irmb) was evaluated in one Phase IIb study (Study 1) and one Phase III study (CLARITY AD).[14,15] Results from Study 1 demonstrated a reduction in amyloid beta plaque which served as the basis for FDA approval under the accelerated approval pathway.

On January 6th, 2023, it was announced that data from the confirmatory CLARITY AD trial was submitted to the FDA as part of a supplemental Biologics License Application (sBLA) to convert the

accelerated approval to a traditional approval. On July 6th, 2023, the FDA converted Leqembi to traditional approval based on the confirmatory trial CLARITY AD.

Study 1

Methods

Patients 50 to 90 years of age were eligible to participate if they met criteria for MCI due to AD or mild AD dementia and had confirmed evidence of beta-amyloid by PET scan or cerebrospinal fluid (CSF) beta-amyloid$_{1-42}$. Additionally, patients had to have objective impairment in episodic memory on Wechsler Memory Scale-IV Logical Memory II, Mini Mental State Examination (MMSE) score greater than or equal to 22. Patients were also required to have a Clinical Dementia Rating Scale global score of 0.5 or 1.0 with a Memory Box score of ≥ 0.5. Patients were excluded from the study for any neurologic condition (other than Alzheimer's disease), history of transient ischemic attacks, stroke, or seizures, or significant pathological findings on brain MRI.

The study included a 2-month screening period, an 18-month (78-week) placebo-controlled treatment period, and a safety follow-up period of 3 months after the final dose. During the placebo-controlled treatment period, patients were randomized to placebo or one of five lecanemab dosing regimen: 3 arms with biweekly (once every 2 weeks) dosing (2.5, 5, and 10 mg/kg) and 2 arms with monthly (once every 4 weeks) dosing (5 and 10 mg/kg). Of note, during the study, the protocol was amended so that ApoE ε4 carriers were no longer randomized to the 10 mg/kg every two weeks dose arm. ApoE ε4 carriers who had been receiving Leqembi 10 mg/kg every two weeks for 6 months or less were discontinued from the study drug. This was based on data indicating that ApoE ε4 homozygotes on the highest dose of Leqembi (10mg/kg once every 2 weeks) had the highest risk of developing symptomatic ARIA-E.

The primary endpoint was change from baseline at 12 months on Alzheimer's Disease Composite Score (ADCOMS). Secondary endpoints included change from baseline at 18 months in brain amyloid by PET Standard Uptake Value ratio (SUVr), score on the ADCOMS, CDR-SB, and ADAS-Cog14.

Results

Leqembi dosed 10 mg/kg once every 2 weeks was identified as the target dose. Leqembi reached a 64% probability of being better than placebo with 25% less decline at 12 months in the ADCOMS, missing the pre-specified 80% probability threshold. Therefore, the primary endpoint was not met.

A total of 315 patients were enrolled in the amyloid PET sub-study and of those 277 had results evaluated at week 79. Lecanemb 10 mg/kg once every 2 weeks had a statistically significant decrease in brain amyloid plaque as measured by PET quantified by a composite SUVr when compared to placebo at Week 79 (-0.310, p<0.001). The FDA concluded, based on the surrogate endpoint of reduction in amyloid plaque burden, there was data to support the accelerated approval of Leqembi.

CLARITY AD

Methods

Eligible patients were 50 to 90 years with MCI or mild AD dementia with confirmed evidence of beta-amyloid by PET scan or cerebrospinal fluid (CSF). Inclusion and exclusion criteria were similar to Study 1.

The trial design included a screening period, followed by an 18-month (78-week) placebo-controlled treatment period, and a safety follow-up period of 3 months. Patient were randomized in a 1:1 fashion to either Leqembi 10 mg/kg IV once every 2 weeks or placebo for 18 months.

The primary efficacy endpoint was change from baseline at Week 78 on the CDR-SB scale, where higher scores indicate greater impairment. Secondary endpoints included change from baseline at 18 months in amyloid on PET scan, score on the ADAS-Cog14, ADCOMS, and Alzheimer's Disease Cooperative Study-Activities of Daily Living-Mild Cognitive Impairment (ADCS-ADL-MCI).

Results

Of the 1,795 participates, 898 received Leqembi and 897 received placebo. Baseline characteristics were similar between the two groups. Of note, 31% of participants were ApoE ε4 noncarriers. At 18 months, the adjusted mean change from baseline in CDR-SB score was 1.21 in the Leqembi arm and 1.66 in the placebo arm (treatment difference of -0.45; 95% confidence interval [CI]: -0.67 to -0.23; $P < 0.001$). The sub-study of amyloid burden on PET included 698 participants and found the adjusted mean change from baseline at 18 months was -55.48 centiloids in the Leqembi arm and 3.64 centiloids in the placebo arm (treatment difference -59.12 centiloids; 95% CI: -62.64, -55.60; P < 0.001).

Leqembi Safety

Similar to Aduhelm, Leqembi carriers a warning regarding ARIA. In Study 1, symptomatic ARIA occurred in 3% of patients treated with Leqembi. Clinical symptoms resolved in 80% of patients during the observation period. When including asymptomatic radiographic events, 12% of Leqembi treated patients versus 5% of patients on placebo had observed ARIA. ARIA-E was seen in 10% of Leqembi treated patients versus 1% in the placebo group. ARIA-H was seen in 6% and 5% of patients treated with Leqembi and placebo, respectively.

ARIA was higher in Leqembi treated patients who were ApoE ε4 homozygotes when compared to heterozygotes and noncarriers. Leqembi prescribing information gives consideration for testing ApoE ε4 status to gauge risk of developing ARIA before starting Leqembi treatment. Additionally, the prescribing information outlines monitoring and dosing interruption protocols for ARIA.

Leqembi can cause infusion-related reactions and may require infusion rate reductions or premedication at subsequent dosing.

The most common adverse reactions in patients treated with Leqembi (incidence approximately 10% and a higher rate compared to placebo): infusion-related reactions (20%), headache (14%), and ARIA-edema (10%).

RATIONALE:

Aduhelm (aducanumab-avwa)
Based on the inconsistencies in ENGAGE and EMERGE clinical trial data for Aduhelm (aducanumab-avwa), there is insufficient data to establish clinically meaningful effectiveness that leads to improved health outcomes for treatment of Alzheimer's disease. Additionally, when taking into consideration the higher incidence of ARIA compared to placebo, there is insufficient evidence to suggest that the clinical benefit of Aduhelm (aducanumab-avwa) outweighs the potential risks of therapy.

Leqembi (lecanemab-irmb)

Pharmacy Management Drug Policy
Anti-Amyloid Directed Therapies

In Study 1, Leqembi (lecanemab-irmb) demonstrated statistically significant reduction in amyloid plaque burden but did not achieve the primary efficacy endpoint. Although CLARITY AD demonstrated a statistically significant reduction of worsening in the CDR-SB score compared to placebo, the absolute difference of 0.45 is less than the minimal clinically important difference (MCID) of 1-2 points cited in the literature.[16,17]

Based on the currently available literature for Leqembi (lecanemab-irmb), there is insufficient data to establish clinically meaningful effectiveness that leads to improved health outcomes for the treatment of Alzheimer's disease. Additionally, when taking into consideration the higher incidence of ARIA compared to placebo, there is insufficient evidence to suggest that the clinical benefit of Leqembi (lecanemab-irmb) outweighs the potential risks of therapy.

POLICY:

Aduhelm (aducanumab-avwa) coverage varies by line of business as below:

Commercial/Essential criteria:

1. Based upon our criteria and assessment of the peer-reviewed evidence, the use of Aduhelm (aducanumab-avwa) has not been medically proven to be effective and, therefore, is considered **investigational** for the treatment of Alzheimer's disease. The justification for Aduhelm (aducanumab-avwa) to be considered investigational is as follows:
   a. Based upon our assessment of the peer-reviewed medical literature, there is inconclusive evidence that the drug has a definite positive effect on health outcomes.
   b. Based upon our assessment of the peer-reviewed medical literature, there is inconclusive evidence that the drug, over time, leads to improvement in health outcomes (e.g., the beneficial effects of the service outweigh any harmful effects).
   c. Based upon our assessment of peer-reviewed medical literature, there is inconclusive evidence that the drug provides improvement in health outcomes in standard conditions of medical practice, outside the clinical investigatory settings.

   Refer to Corporate Medical Policy #11.01.03 Experimental or Investigational Services

Medicare criteria:

1. Medicare reviews are to follow the national coverage determination (NCD) issued by CMS effective 12/12/2022**.** The NCD can be found on the CMS website at: https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=375&ncdver=1

Medicaid criteria:

1. Prescriber must attest that the patient has been diagnosed with mild cognitive impairment due to Alzheimer's Disease or mild Alzheimer's dementia by meeting one of the following:
   a. Clinical Dementia Rating (CDR) Global score of 0.5 to 1
   b. Mini-Mental Status Exam (MMSE) score between 24 and 30
   c. Montreal Cognitive Assessment (MoCA) score of at least 18
2. Prescriber must provide medical records for the following pre-treatment testing:
   a. Genetic testing to assess apolipoprotein E ε4 (ApoE ε4) AND
   b. Positron emission tomography (PET) scan or cerebrospinal fluid (CSF) analysis to confirm that presence of amyloid beta deposit

3. Prescriber must attest that the patient does not have any evidence of any medical or neurological condition other than Alzheimer's Disease that could be contributing to the patient's cognitive impairment
4. Prescriber must attest that the patient does not have a history of a clotting disorder and is not taking any form of antiplatelet or anticoagulant medications other than aspirin ≤ 325 mg per day
5. For continuation of therapy, the provider must attest that the patient's score remained stable or improved, utilizing the same baseline assessment tool provided on initial review

Leqembi (lecanemab-irmb) coverage varies by line of business as below:

Commercial/Essential/Medicaid criteria:

1. Based upon our criteria and assessment of the peer-reviewed evidence, the use of Leqembi (lecanemab-irmb) has not been medically proven to be effective and, therefore, is considered **investigational** for the treatment of Alzheimer's disease. The justification for Leqembi (lecanemab-irmb) to be considered investigational is as follows:
   a. Based upon our assessment of the peer-reviewed medical literature, there is inconclusive evidence that the drug has a definite positive effect on health outcomes.
   b. Based upon our assessment of the peer-reviewed medical literature, there is inconclusive evidence that the drug, over time, leads to improvement in health outcomes (e.g., the beneficial effects of the service outweigh any harmful effects).
   c. Based upon our assessment of peer-reviewed medical literature, there is inconclusive evidence that the drug provides improvement in health outcomes in standard conditions of medical practice, outside the clinical investigatory settings.

Refer to Corporate Medical Policy #11.01.03 Experimental or Investigational Services

Medicare criteria:

Medicare reviews are to follow the national coverage determination (NCD) issued by CMS effective 12/12/2022. The NCD can be found on the CMS website at: https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=375&ncdver=1

POLICY GUIDELINES:

1. Approval will be granted for 1 year if the above criteria are satisfied
2. Prior authorization is contract dependent
3. Not all contracts cover all Medical Infusible drugs. Refer to specific contract/benefit plan language for exclusions of Injectable Medications.
4. Aduhelm and Leqembi are administered intravenously and will be considered for coverage under the medical benefit.

CODES:

Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract. Codes may not be covered under all circumstances. Please read the policy and guidelines statements carefully.
Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.
Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).
Copyright © 2006 American Medical Association, Chicago, IL

Pharmacy Management Drug Policy
Anti-Amyloid Directed Therapies

HCPCS:

Drug Name	J-Code (if assigned)	NDC
Aduhelm	J0172	64406-101-01 64406-102-02
Leqembi	J0174	62856-0212-01 62856-0215-01

UPDATES:

Date	Revision
9/23	Revised/P&T Approval 08/24/2023
7/23	Revised
2/23	Revised / P&T Committee Approval 02/9/2023
12/22	Revised
8/22	Revised
7/22	P&T Committee Approval
2/22	Revised
1/22	Revised
9/21	Revised
7/21	P&T Committee Approval
7/21	Revised
6/21	Created

REFERENCES:

1. 2021 Alzheimer's disease facts and figures. Alzheimer's & dementia: the journal of the Alzheimer's Association. 2021;17(3):327-406.
2. Boyle PA, Lei Y, Wilson RS, Leurgans SE, Schneider JA, Bennett DA. Person-specific contribution of neuropathologies to cognitive loss in old age. Ann Neurol. 2018;83(1):74-83.
3. Du X, Wang X, Geng M. Alzheimer's disease hypothesis and related therapies. Translational Neuorodegeneration. 2018;7:2.
4. Rajmohan R, Reddy PH. Amyloid-Beta and Phosphorylated Tau Accumulations Cause Abnormalities at Synapses of Alzheimer's disease Neurons. J Alzheimers Dis. 2017;57(4):975-999.
5. Lozupone M, Solfrizzi V, Durso F, et al. Anti-amyloid-B protein agents for the treatment of Alzheimer's disease: an update on emerging drugs. Expert Opinion on Emerging Drugs.2020;25:3.319-335.
6. Aduhelm™ intravenous infusion [prescribing information]. Cambridge, MA: Biogen; Revised July 2021. Accessed July 8, 2021.
7. FDA's Decision to Approve New Treatment for Alzheimer's Disease. FDA website. https://www.fda.gov/drugs/news-events-human-drugs/fdas-decision-approve-new-treatment-alzheimers-disease. Published June 7, 2021. Accessed June 14, 2021.
8. Accelerated Approval Program. FDA website. https://www.fda.gov/drugs/information-health-care-professionals-drugs/accelerated-approval-program. Content current as of October 26, 2020. Accessed June 14, 2021.
9. Combined FDA and Biogen Briefing Information for the November 6, 2020Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee. FDA website.

https://www.fda.gov/advisory-committees/advisory-committee-calendar/november-6-2020-meeting-peripheral-and-central-nervous-system-drugs-advisory-committee-meeting#event-materials. Content current as of 2/5/21. Accessed June 14, 2021.

10. Budd Haeberlein S, Aisen PS, Barkhof F, et al. Two randomized phase 3 studies of aducanumab in early Alzheimer's Disease. J Prev Alzheimers Dis. 2022;2(9):197-210.
11. Minutes for the November 6,2020 Meeting of the Peripheral and Central Nervous System Advisory Committee. FDA website. https://www.fda.gov/advisory-committees/advisory-committee-calendar/november-6-2020-meeting-peripheral-and-central-nervous-system-drugs-advisory-committee-meeting#event-materials. Content current as of February 5, 2021. Accessed June 14, 2021.
12. Lin GA, Whittington MD, Synnott PG, McKenna A, Campbell J, Pearson SD, Rind DM. Aducanumab for Alzheimer's Disease: Effectiveness and Value; Evidence Report. Institute for Clinical and Economic Review, June 30, 2021. https://icer.org/assessment/alzheimers-disease-2021/. Accessed July 7, 2021.
13. ICER Issues Statement on the FDA's Approval of Aducanumab for Alzheimer's Disease. https://icer.org/news-insights/press-releases/icer-issues-statement-on-the-fdas-approval-of-aducanumab-for-alzheimers-disease/ Published June 7, 2021. Accessed June 14, 2021.
14. Swanson CJ, Zhang Y, Dhadda S, et al. A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody. Alzheimers Res Ther 2021;13(1):80.
15. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. N Engl J Med. 2023;388(1):9-21.
16. Liu KY, Schneider LS, Howard R. The need to show minimum clinically important differences in Alzheimer's disease trials. Lancet Psychiatry. 2021;8(11):1013-1016.
17. Andrews JS, Desai U, Kirson NY, et al. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. Alzheimers Dement. 2019;5:354-363.