EFFECTIVE DATE: 01|01|2022
POLICY LAST UPDATED: 12|30|2021

OVERVIEW

Alzheimer disease is a neurodegenerative disorder leading to progressive, irreversible destruction of neurons and loss of cognitive function and memory. Over time, patients progress to severe dementia, loss of independence, and death. Extracellular deposits of amyloid beta (A-β), referred to as amyloid plaques are considered a hallmark of the disease. Beta-amyloid monomers lead to formation of beta oligomers and fibrils and are deposited as plaques and then interact with tau fibrils, leading to formation of neuro-fibrillatory tangles. These pathophysiological changes and clinical manifestations of Alzheimer disease are progressive and occur along a continuum, and accumulation of A-β may begin 20 years or more before symptoms arise. Aducanumab is a human IgG1 anti-A-β antibody targeting amyloid aggregates. The drug is administered by intravenous infusion every 4 weeks. Binding of antibody is intended to lead to clearance of amyloid from the brain. On June 7, 2021, the U.S. Food and Drug Administration approved Aduhelm (aducanumab) for the treatment of Alzheimer disease. It was approved under accelerated approval based on reduction in A-β plaques observed in patients treated with aducanumab. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial.

MEDICAL CRITERIA

Not applicable

PRIOR AUTHORIZATION

Not applicable

POLICY STATEMENT

Medicare Advantage Plans

The use of aducanumab is not covered for all indications including treatment of Alzheimer disease, as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Commercial Products

The use of aducanumab is not medically necessary for all indications including treatment of Alzheimer disease, as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

COVERAGE

Benefits may vary between groups/contracts. Please refer to the appropriate Evidence of Coverage for applicable not medically necessary/not covered benefits/coverage.

BACKGROUND

Alzheimer Disease

Alzheimer disease is a fatal neurodegenerative disease that causes progressive loss in memory, language, and thinking, with the eventual loss of ability to perform social and functional activities in daily life. Survival after a diagnosis of dementia due to Alzheimer disease generally ranges between 4 and 8 years; however, life expectancy can be influenced by other factors, such as comorbid medical conditions. It is estimated that 6.2 million Americans aged 65 and older are currently living with Alzheimer disease dementia, and the number is projected to reach over 12 million by 2050.

Pathophysiology

The pathologic hallmarks of Alzheimer disease are extracellular deposits of beta-amyloid (A-β), referred to as amyloid plaques, and intracellular aggregates of hyperphosphorylated tau in the form of neurofibrillary tangles. There are different forms of amyloid such as plaques, oligomers, and monomers, and the roles of these different forms and how specifically they are pathophysiologically associated with Alzheimer disease is not well understood. Generally referred to as "amyloid hypothesis", it is believed that aggregation of A-β oligomers in the brain leads to amyloid plaques and thought to be the primary driver of the disease process. Amyloid aggregation is thought to precede accumulation of tau pathology and neurodegeneration. These changes in the brain result in widespread neurodegeneration and cell death, and ultimately cause the clinical signs and symptoms of dementia.

Salient known risk factors for Alzheimer disease are older age, genetics, and family history. Of these, increasing age has the largest known impact on risk of developing Alzheimer disease. While several genes have been found to increase the risk of Alzheimer disease, the ε4 allele of the apolipoprotein E (*ApoE*) gene is the strongest known genetic risk factor. Having 1 copy of the gene is associated with a 2- to 3-fold increase in developing Alzheimer disease while 2 copies of the gene may increase risk of Alzheimer disease by as much as 15 times. Approximately two-thirds of pathology-confirmed Alzheimer disease cases are ε4 positive (homozygous or heterozygous), compared with about 15% to 20% of the general population. Autosomal dominant genetic mutations are estimated to account for less than 1% of Alzheimer disease cases.

The pathophysiological changes and clinical manifestations of Alzheimer disease are progressive and occur along a continuum, and accumulation of A-β may begin 20 years or more before symptoms arise. National Institute on Aging-Alzheimer's Association (NIA-AA) have created a "numeric clinical staging scheme" (Table 1) that avoids traditional syndromal labels and is applicable for only those in the Alzheimer continuum. This staging scheme reflects the sequential evolution of Alzheimer disease from an initial stage characterized by the appearance of abnormal Alzheimer disease biomarkers in asymptomatic individuals. As biomarker abnormalities progress, the earliest subtle symptoms become detectable. Further progression of biomarker abnormalities is accompanied by progressive worsening of cognitive symptoms, culminating in dementia. This numeric cognitive staging scheme is not designed to be used in a clinical setting but to be used for interventional trials such as those of aducanumab. The phase 3 randomized controlled trials for aducanumab were stratified to include 80% of stage 3 patients and 20% of stage 4 patients. This numeric staging scheme is very similar to the categorical system for staging Alzheimer disease outlined in the Food and Drug Administration (FDA) guidance for industry pertaining to developing drugs for treatment of early Alzheimer disease.

Many tests are available in the market to detect the underlying core pathology such use of certain biomarkers in the cerebrospinal fluid (CSF) (eg, decreased A-β and increased CSF tau protein levels) and on imaging (e.g., amyloid on positron emission tomography [PET] scans). Approved amyloid PET tracers in the US include [18F]-florbetapir, [18F]-flutemetamol and [18F]-florbetaben. In addition, there are several CSF tests for A-β confirmation that are currently in development in the US. CSF tests and amyloid PET tracers are routinely used in the enrollment of participants in contemporary Alzheimer disease studies.

Current Treatment

Current treatment goals for patients with Alzheimer disease are often directed to maintain quality of life, treat cognitive symptoms, and manage behavioral and psychological symptoms of dementia. Treatment remains largely supportive, including creation and implementation of individualized dementia care plans, caregiver education and support, care navigation, care coordination, and referral to community-based organizations for services (eg, adult day care, caregiver training, etc). Non-pharmacologic treatments include physical activity as well as behavioral strategies to ameliorate neuropsychiatric symptoms (eg, agitation, delusions, disinhibition), and problem behaviors (eg, resistance to care, hoarding, obsessive-compulsive behaviors). Currently FDA-approved drugs for Alzheimer include cholinesterase inhibitors donepezil, rivastigmine, and galantamine, and the N-methyl-D-aspartate antagonist memantine. Cholinesterase inhibitors are indicated in mild, moderate,

and severe AD, while memantine is approved for moderate-to-severe AD. These drugs, either alone or in combination, focus on managing cognitive and functional symptoms of the disease and have not been shown to alter disease trajectory. The evidence for efficacy is limited and associated with significant side effects.

Regulatory Status
In June 2021, aducanumab (Aduhelm; Biogen) was approved by the U.S. FDA for treatment of Alzheimer disease. This indication was approved under accelerated approval based on reduction in A-β plaques observed in patients treated with aducanumab. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

In July 2021, FDA amended the approved label to emphasize the disease stages studied in the clinical trials. The amended label states, "Treatment with aducanumab 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."

The FDA, under the accelerated approval regulations (21 CFR 601.41), requires that Biogen conduct a randomized, controlled trial to evaluate the efficacy of aducanumab-avwa compared to an appropriate control for the treatment of Alzheimer disease. The trial should be of sufficient duration to observe changes on an acceptable endpoint in the patient population enrolled in the trial. The expected date of trial completion is August 2029 and final report submission to the FDA by February 2030.

For individuals with early Alzheimer disease (mild cognitive impairment [MCI] or mild dementia due to Alzheimer disease) who receive aducanumab, the evidence includes 2 randomized controlled trials (RCTs) and 1 dose-finding and proof of concept phase I trial. Relevant outcomes are disease-specific survival, change in disease status, functional outcomes, health status measures, quality of life, and treatment-related mortality and morbidity. ENGAGE (study 301) and EMERGE (study 302) were identical randomized, double-blind, placebo-controlled studies that enrolled patients with early Alzheimer disease. The majority of patients had a diagnosis of MCI due to Alzheimer disease (81.6%) and approximately two-thirds were *apolipoprotein E ε4* carriers. The primary clinical outcome was change in mean score on the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB). Both trials were terminated early following a prespecified interim analysis for futility. In study 301, there was no treatment benefit observed in either the high- or low-dose arms at week 78. In study 302, a statistically significant difference in change from baseline in CDR-SB was observed in the high-dose arm (difference vs. placebo -0.39 [95% confidence interval, -0.69 to -0.09]) but not the low-dose arm at week 78. The observed change of 0.39 was well below the range of 1 to 2 points reported as the minimal clinically important difference in published literature. Approval by the FDA was based on the reduction in A-β plaques, which was observed in both trials and at all doses. However, there are no satisfactory data clearly establishing that individual changes in amyloid correlate with or predict long term cognitive and functional changes. In the absence of clinical data convincingly demonstrating a clinical effect, it cannot be concluded that the observed reduction in amyloid will translate into a clinical benefit to patients. Cognitive decline in early Alzheimer disease generally occurs over years, and thus the follow-up duration may not be sufficient to conclude whether a drug is effective for this disease or whether the safety profile might change with longer follow-up. Pooled safety data showed that about 35% of patients on aducanumab experienced amyloid-related imaging abnormalities (ARIA) as well an increase in the risk of falling. A confirmatory, prospective and adequately powered trial is necessary to assess the net health benefit of aducanumab in patients with early Alzheimer disease. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

CODING

Medicare Advantage Plans and Commercial Products
J0172 Injection, aducanumab-avwa, 2 mg (New Code Effective 1/1/2022)

For dates of service prior to 1/1/2022, there is no specific HCPCS code assigned to Aduhelm (Aducanumab). Therefore, an appropriate Unlisted HCPCS code **and** National Drug Code (NDC) must be filed.

RELATED POLICIES
Not applicable

PUBLISHED
Provider Update, November 2021

REFERENCES

1. 2021 Alzheimer's disease facts and figures. Alzheimers Dement. Mar 2021; 17(3): 327-406. PMID 33756057
2. Alzheimer's Association. 2021 Alzheimers disease facts and figures. Published 2021. Available at https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf. Accessed June 28, 2021.
3. Roberts RO, Aakre JA, Kremers WK, et al. Prevalence and Outcomes of Amyloid Positivity Among Persons Without Dementia in a Longitudinal, Population-Based Setting. JAMA Neurol. Aug 01 2018; 75(8): 970-979. PMID 29710225
4. Elias-Sonnenschein LS, Viechtbauer W, Ramakers IH, et al. Predictive value of APOE-4 allele for progression from MCI to AD-type dementia: a meta-analysis. J Neurol Neurosurg Psychiatry. Oct 2011; 82(10): 1149-56. PMID 21493755
5. Mattsson N, Groot C, Jansen WJ, et al. Prevalence of the apolipoprotein E 4 allele in amyloid positive subjects across the spectrum of Alzheimer's disease. Alzheimers Dement. Jul 2018; 14(7): 913-924. PMID 29601787
6. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA. Oct 1997; 278(16): 1349-56. PMID 9343467
7. Bekris LM, Yu CE, Bird TD, et al. Genetics of Alzheimer disease. J Geriatr Psychiatry Neurol. Dec 2010; 23(4): 213-27. PMID 21045163
8. Vermunt L, Sikkes SAM, van den Hout A, et al. Duration of preclinical, prodromal, and dementia stages of Alzheimer's disease in relation to age, sex, and APOE genotype. Alzheimers Dement. Jul 2019; 15(7): 888-898. PMID 31164314
9. US Food and Drug Administration. Early Alzheimers disease: developing drugs for treatment guidance for industry. Draft Guidance. Published online Feb 29, 2018. Available at https://www.fda.gov/media/110903/download. Accessed on June 28, 2021
10. Combined FDA and Applicant PCNS Drugs Advisory Committee Briefing Document: Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee Meeting- November 6, 2020. Available at https://www.fda.gov/media/143502/download Accessed June 28 2021
11. Reuben DB, Tan ZS, Romero T, et al. Patient and Caregiver Benefit From a Comprehensive Dementia Care Program: 1-Year Results From the UCLA Alzheimer's and Dementia Care Program. J Am Geriatr Soc. Nov 2019; 67(11): 2267-2273. PMID 31355423
12. Gronek P, Balko S, Gronek J, et al. Physical Activity and Alzheimer's Disease: A Narrative Review. Aging Dis. Dec 2019; 10(6): 1282-1292. PMID 31788339
13. Du Z, Li Y, Li J, et al. Physical activity can improve cognition in patients with Alzheimer's disease: a systematic review and meta-analysis of randomized controlled trials. Clin Interv Aging. 2018; 13: 1593-1603. PMID 30233156
14. Gitlin LN, Kales HC, Lyketsos CG. Nonpharmacologic management of behavioral symptoms in dementia. JAMA. Nov 21 2012; 308(19): 2020-9. PMID 23168825
15. Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt HP, et al. Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials. BMJ. Aug 06 2005; 331(7512): 321-7. PMID 16081444
16. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement. Apr 2018; 14(4): 535-562. PMID 29653606
17. US Food and Drug Administration. Draft guidance for industry on Alzheimers disease: developing drugs for the treatment of early stage disease. Published online March 28, 2013. Available at

https://isctm.org/public_access/FDAGuidance_AD_Developing_Drugs_Early_Stage_Treatment.pdf. Accessed on June 29, 2021
18. Liu KY, Schneider LS, Howard R. The need to show minimum clinically important differences in Alzheimer's disease trials. Lancet Psychiatry. Jun 01 2021. PMID 34087114
19. Cedarbaum JM, Jaros M, Hernandez C, et al. Rationale for use of the Clinical Dementia Rating Sum of Boxes as a primary outcome measure for Alzheimer's disease clinical trials. Alzheimers Dement. Feb 2013; 9(1 Suppl): S45-55. PMID 22658286
20. 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 (N Y). 2019; 5: 354-363. PMID 31417957
21. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. Nov 1975; 12(3): 189-98. PMID 1202204
22. Chapman KR, Bing-Canar H, Alosco ML, et al. Mini Mental State Examination and Logical Memory scores for entry into Alzheimer's disease trials. Alzheimers Res Ther. Feb 22 2016; 8: 9. PMID 26899835
23. Franco-Marina F, Garcia-Gonzalez JJ, Wagner-Echeagaray F, et al. The Mini-mental State Examination revisited: ceiling and floor effects after score adjustment for educational level in an aging Mexican population. Int Psychogeriatr. Feb 2010; 22(1): 72-81. PMID 19735592
24. Galasko D, Abramson I, Corey-Bloom J, et al. Repeated exposure to the Mini-Mental State Examination and the Information-Memory-Concentration Test results in a practice effect in Alzheimer's disease. Neurology. Aug 1993; 43(8): 1559-63. PMID 8351011
25. Spencer RJ, Wendell CR, Giggey PP, et al. Psychometric limitations of the mini-mental state examination among nondemented older adults: an evaluation of neurocognitive and magnetic resonance imaging correlates. Exp Aging Res. 2013; 39(4): 382-97. PMID 23875837
26. Mohs RC, Knopman D, Petersen RC, et al. Development of cognitive instruments for use in clinical trials of antidementia drugs: additions to the Alzheimer's Disease Assessment Scale that broaden its scope. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord. 1997; 11 Suppl 2: S13-21. PMID 9236948
27. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry. Nov 1984; 141(11): 1356-64. PMID 6496779
28. Schrag A, Schott JM. What is the clinically relevant change on the ADAS-Cog?. J Neurol Neurosurg Psychiatry. Feb 2012; 83(2): 171-3. PMID 22019547
29. McDougall F, Edgar C, Mertes M, et al. Psychometric Properties of the Clinical Dementia Rating - Sum of Boxes and Other Cognitive and Functional Outcomes in a Prodromal Alzheimer's Disease Population. J Prev Alzheimers Dis. 2021; 8(2): 151-160. PMID 33569561
30. Vellas B, Bateman R, Blennow K, et al. Endpoints for Pre-Dementia AD Trials: A Report from the EU/US/CTAD Task Force. J Prev Alzheimers Dis. Jun 2015; 2(2): 128-135. PMID 26247004
31. Bullock R, Touchon J, Bergman H, et al. Rivastigmine and donepezil treatment in moderate to moderately-severe Alzheimer's disease over a 2-year period. Curr Med Res Opin. Aug 2005; 21(8): 1317-27. PMID 16083542
32. Tariot PN, Solomon PR, Morris JC, et al. A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. Neurology. Jun 27 2000; 54(12): 2269-76. PMID 10881251
33. Doody RS, Thomas RG, Farlow M, et al. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. N Engl J Med. Jan 23 2014; 370(4): 311-21. PMID 24450890
34. Cummings J. The Neuropsychiatric Inventory: Development and Applications. J Geriatr Psychiatry Neurol. Mar 2020; 33(2): 73-84. PMID 32013737
35. Howard R, Phillips P, Johnson T, et al. Determining the minimum clinically important differences for outcomes in the DOMINO trial. Int J Geriatr Psychiatry. Aug 2011; 26(8): 812-7. PMID 20848576
36. Sevigny J, Chiao P, Bussiere T, et al. The antibody aducanumab reduces A plaques in Alzheimer's disease. Nature. Sep 01 2016; 537(7618): 50-6. PMID 27582220
37. FDA Pre-Recorded Presentation Slides for the November 6, 2020: Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee. Available at https://www.fda.gov/media/143504/download. Accessed on June 28, 2021

38. Prescribing Label: ADUHELM (aducanumab-avwa) injection, for intravenous use Available at https://www.biogencdn.com/us/aduhelm-pi.pdf. Accessed on June 28, 2021
39. Biogen Presentation for the November 6, 2020: Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee. Available at https://www.fda.gov/media/143577/download. Accessed on June 28, 2021
40. Aducanumab for Alzheimers Disease: Effectiveness and Value- Draft Evidence Review. Institute for Clinical and Economic Review (ICER). Available at https://icer.org/wp-content/uploads/2020/10/ICER_ALZ_Draft_Evidence_Report_050521.pdf. Accessed on June 29, 2021