MASSACHUSETTS

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Medical Policy

# Aducanumab for Alzheimer Disease

## Table of Contents



## Policy Number: 946

BCBSA Reference Number: 5.01.38 (For Plan internal use only)
NCD/LCD: N/A

## Related Policies

None

## Policy

### Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue℠ and Medicare PPO Blue℠ Members

The use of aducanumab is considered **INVESTIGATIONAL** for all indications including treatment of Alzheimer disease.

## Prior Authorization Information

**Inpatient**

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

**Outpatient**

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

| | Outpatient |
|---|---|
| **Commercial Managed Care (HMO and POS)** | This is **not** a covered service. |
| **Commercial PPO and Indemnity** | This is **not** a covered service. |
| **Medicare HMO Blue℠** | This is **not** a covered service. |
| **Medicare PPO Blue℠** | This is **not** a covered service. |

## CPT Codes / HCPCS Codes / ICD Codes

*Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.*

*Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.*

*The following codes are included below for informational purposes only; this is not an all-inclusive list.*

**The following HCPCS code is considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:**

## HCPCS Codes

| HCPCS codes: | Code Description |
|---|---|
| J0172 | Injection, aducanumab-avwa, 2 mg |

## Description

**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.[1]

**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.[2,3]

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.[4,5] 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.[6] 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.[5] Autosomal dominant genetic mutations are estimated to account for less than 1% of Alzheimer disease cases.[7]

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.8, 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.[9]

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.[10]

**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).[11] Non-pharmacologic treatments include physical activity[12,13] as well as behavioral strategies to ameliorate neuropsychiatric symptoms (eg, agitation, delusions, disinhibition), and problem behaviors (eg, resistance to care, hoarding, obsessive-compulsive behaviors).[14] 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.[14,15]

Table 1. National Institute on Aging-Alzheimer's Association Numerical Clinical Staging for Individuals in the Alzheimer Continuum[a]

| **Severity Clinical Features** |
|---|
| **Stage 1: Pre-clinical** |
| ▪ Performance within expected range on objective cognitive tests.<br>▪ No evidence of recent cognitive decline or new neurobehavioral symptoms. |
| **Stage 2: Pre-clinical** |
| ▪ Normal performance within expected range on objective cognitive tests.<br>▪ Transitional cognitive decline (change from individual baseline within past 1 to 3 years, and persistent for at least 6 months).<br>▪ Mild neurobehavioral changes may coexist or may be the primary complaint rather than cognitive.<br>▪ No functional impact on daily life activities. |
| **Stage 3: Mild Cognitive Impairment (MCI) due to Alzheimer disease** |
| ▪ Performance in the impaired/abnormal range on objective cognitive tests.<br>▪ Evidence of decline from baseline.<br>▪ Performs daily life activities independently, but cognitive difficulty may result in detectable but mild functional impact on the more complex activities of daily life. |
| **Stage 4: Mild Dementia** |
| ▪ Substantial progressive cognitive impairment affecting several domains, and/or neurobehavioral disturbance.<br>▪ Clearly evident functional impact on daily life, affecting mainly instrumental activities.<br>▪ No longer fully independent/requires occasional assistance with daily life activities. |
| **Stage 5: Moderate Dementia** |
| ▪ Progressive cognitive impairment or neurobehavioral changes.<br>▪ Extensive functional impact on daily life with impairment in basic activities.<br>▪ No longer independent and requires frequent assistance with daily life activities. |
| **Stage 6: Severe Dementia** |
| ▪ Progressive cognitive impairment or neurobehavioral changes.<br>▪ Clinical interview may not be possible. |

| |
|---|
| ▪ Complete dependency due to severe functional impact on daily life with impairment in basic activities, including basic self-care. |

Adapted from Table 6, Jack et al (2018)[16]

[a]Applicable only to individuals in the Alzheimer continuum that fall into 1 of the 4 biomarker groups:

1. A+T+N+
2. A+T-N-
3. A+T+N-
4. A+T-N+ where A: Aggregated Aβ or associated pathologic state (CSF Aβ42, or Aβ42/Aβ40 ratio or Amyloid PET), T: Aggregated tau (neurofibrillary tangles) or associated pathologic state (CSF phosphorylated tau or Tau PET) and N: Neurodegeneration or neuronal injury (anatomic MRI, FDG PET or CSF total tau)

- For stages 1 to 6: Cognitive test performance may be compared to normative data of the investigators choice, with or without adjustment (choice of the investigators) for age, sex, education, etc.
- For stages 2 to 6: Although cognition is the core feature, neurobehavioral changes—for example, changes in mood, anxiety, or motivation—may coexist.
- For stages 3 to 6: Cognitive impairment may be characterized by presentations that are not primarily amnestic.

CSF: cerebrospinal fluid; FDG: fluorodeoxyglucose; MCI: mild cognitive impairment; MRI: magnetic resonance imaging; PET: positron emission tomography.

## Summary

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.

**Summary of Evidence:** 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.

## Policy History

| Date | Action |
|---|---|
| 1/2022 | Clarified coding information. |
| 10/2021 | New medical policy describing investigational indications. The use of aducanumab is considered investigational for all indications including treatment of Alzheimer disease. Effective 10/8/2021. |

## Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

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