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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-fibrillary 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, 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, 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 $\epsilon 4$ 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 $\epsilon 4$ 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* $\epsilon 4$ 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

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

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