Aduhelm (aducanumab-avwa)

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BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

This Medical Policy document describes the status of medical technology at the time the document was developed. Since that time, new technology may have emerged or new medical literature may have been published. This Medical Policy will be reviewed regularly and be updated as scientific and medical literature becomes available.

DESCRIPTION

Aduhelm (aducanumab-avwa) is an amyloid beta-directed antibody indicated for the treatment of Alzheimer's disease. It is administered every 4 weeks as an intravenous (IV) infusion.

This indication was approved by the Food and Drug Administration (FDA) in June 2021 under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with Aduhelm. On July 8, 2021, the FDA approved an updated label that recommends the treatment be used only by Alzheimer's 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. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

POLICY

Aduhelm (aducanumab-avwa) is considered **not medically necessary** for all indications, including the treatment for Alzheimer's disease, due to insufficient evidence to demonstrate clinical efficacy, conflicting clinical results from identically designed studies, and important safety concerns.

CLINICAL RATIONALE

On June 7, 2021, the U.S. Food and Drug Administration (FDA) approved the monoclonal antibody, Aduhelm (aducanumab), for the treatment of Alzheimer's Disease (AD), a neurodegenerative disorder resulting in progressive cognitive and behavioral decline, based on the surrogate endpoint of reduction of amyloid beta plaque in the brain. On July 8, 2021, the FDA approved an updated label that recommends the treatment be used only by Alzheimer's 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. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s). This was a significant change, as the original Aduhelm label on June 7th was the broadest indication the FDA could have approved and would have allowed use in anyone with a diagnosis of Alzheimer's disease, even though the treatment had not been studied in those with moderate or advanced disease.

The approval of Aduhelm comes after an FDA Peripheral and Central Nervous System Drugs Advisory Committee, consisting of a panel of outside advisers, reviewed the available evidence on the drug in November 2020 and voted almost unanimously against approval of Aduhelm.

Efficacy

The efficacy of Aduhelm was evaluated in two identical, 18-month, multinational, randomized, double-blind, unpublished, placebo-controlled phase III studies [EMERGE (N = 1,643) and ENGAGE (N = 1,653)]. The studies randomized patients with early AD (i.e., mild cognitive impairment [MCI] or mild dementia due to AD) to low- or high-dose aducanumab or placebo (exact dosing depended on presence or absence of a genetic marker of AD risk, apolipoprotein $\varepsilon\varepsilon$4 [APOE $\varepsilon\varepsilon$4]). Patients on blood thinners and patients with a history of cardiovascular disease (i.e., unstable angina, MI, advanced chronic HF, conduction abnormalities) were notable exclusions.

EMERGE and ENGAGE have conflicting clinical results. Both studies were terminated prior to their planned completion date after performing a futility analysis that found they were unlikely to meet their primary objective. However, a later analysis based on additional follow-up data, showed that EMERGE met its primary efficacy endpoint. The primary efficacy endpoint was the change from baseline on the Clinical Dementia Rating-Sum of Boxes (CDR-SB) at Week 78. While patients in EMERGE who received high-dose Aduhelm experienced a statistically significant change in CDR-SB compared with placebo (22% less dementia progression vs to placebo), the change was not statistically significant for the high-dose Aduhelm group in ENGAGE (2% increase in dementia progression vs placebo). Those treated with low dose in both trials did not demonstrate a significant difference in dementia progression as compared to placebo. Analysis of secondary endpoints were consistent with the primary endpoint result in each trial (statistically significant differences from placebo in EMERGE, not statistically significant in ENGAGE).

A subgroup of patients from EMERGE and ENGAGE studies were evaluated for changes in key biomarkers using positron emission tomography (PET) and cerebrospinal fluid assays. Individuals receiving high dose Aduhelm demonstrated significant reductions in beta amyloid plaques compared with placebo. This reduction in beta amyloid, a surrogate marker for Alzheimer's disease pathology, was the basis for accelerated approval. Per the FDA, a surrogate endpoint is a marker that is thought to predict clinical benefit but is not itself a measure of clinical benefit.

Safety

Aduhelm can cause amyloid related imaging abnormalities-edema (ARIA-E), which can be observed on magnetic resonance imaging (MRI) as brain edema or sulcal effusions, and amyloid related imaging abnormalities-hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis.

A brain MRI should be obtained within one year prior to initiating treatment. The safety of Aduhelm in patients with any pre- treatment localized superficial siderosis, 10 or more brain microhemorrhages, and/or with a brain hemorrhage greater than 1 cm within one year of treatment initiation has not been established.

Warnings and precautions for Aduhelm include amyloid-related imaging abnormalities (ARIA) and hypersensitivity reactions. The most common adverse reactions (> 10% and higher incidence compared to placebo) with Aduhelm use were ARIA-edema (ARIA-E), headache, ARIA-hemosiderin deposition (ARIA-H) microhemorrhage, ARIA-H superficial siderosis, and falls.

AAN Position Statement

The American Academy of Neurology (AAN) published a position statement on November 17, 2021, with the purpose to offer ethical guidance on how neurologists can help patients make informed decision about treatment with Aduhelm. Ethical guidance in the position statement says it is important to communicate to people that Aduhelm will not cure Alzheimer's disease and does not restore cognitive function. The statement noted that while Aduhlem reduces the beta-amyloid plaques in the brain that are markers of Alzheimer's, it's unclear whether that provides any meaningful benefits to patients. It also says there are insufficient grounds to warrant offering it to people with moderate or advanced dementia due to Alzheimer's disease, or by patients without biomarker evidence of brain beta-amyloid.

Due to the risk of brain inflammation and brain bleeds, which occurred in a third of patients in the studies who received the dose approved by the FDA, the AAN statement said neurologists must inform patients and families about the drug's potential risks of and the need for more frequent monitoring with MRI scans. The statement also said that patients in racial and ethnic minorities need to be told about the lack of safety and effectiveness data for them.

In summary, the clinical benefit of treatment for Alzheimer's disease with Aduhelm has not been demonstrated and there are serious adverse events associated with its use. The establishment of a clinical benefit, including improved cognitive function or slowing the decline of cognitive function, is warranted in on-going clinical trials. The following conclusion is also stated in the FDA prescribing information, "Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s)". No timeline is available for the completion of the confirmatory trial(s).

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- J0172 Injection, aducanumab-avwa, 2 mg (effective 1/1/2022)

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POLICY HISTORY

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