Medical Policy Reference Manual
Medical Policy

5.01.043 Aducanumab (Aduhelm™)

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Description

Alzheimer's disease is characterized by deposition of amyloid-β plaques (Aβ) and neurofibrillary tangles in the brain. Synaptic dysfunction and neurodegeneration occur alongside the accumulation of plaques and tangles. It has been hypothesized that accumulation of Aβ is responsible for the decline in function that is observed in patients with Alzheimer's disease. Aducanumab is a human monoclonal antibody that selectively targets aggregated Aβ. It enters the brain at low concentrations, binds to amyloid plaques and amyloid oligomers, and stimulates microglia to clear the amyloid species.

The question of whether progression of Alzheimer's disease is slowed through Aβ immunotherapy is a topic of debate. Some studies have revealed a lack of efficacy of pathology-targeted treatment in affecting symptoms. The high doses of medication that are necessary to have an impact on Aβ plaque formation have also been found to cause encephalomeningitis, thus preventing immunotherapies from being administered at efficacious doses. Because the Aβ protein acts synergistically with the tau protein, it is possible that both factors should be targeted to produce a clinical benefit. Although biomarkers for Alzheimer's disease have been clearly identified yet the disease remains a complex and multifaced disorder. Currently, there is debate among experts in the Alzheimer's community about the stage at which Alzheimer's disease is reversible.

Policy

For Medicare Advantage, refer to CareFirst Policy MA MRA 1.00, *Medicare Advantage National and Local Coverage Determinations*. If a relevant National Coverage Determination (NCD) or Local Coverage Determination (LCD) does not exist, this policy will guide coverage determination.

Aducanumab is considered **experimental / investigational** for all indications, including Alzheimer's disease, as it does not meet TEC criteria # 2-5.

Policy Guidelines

Experimental/Investigational

The term "experimental/investigational" describes services or supplies that are in the developmental stage and are in the process of human or animal testing. Services or supplies that do not meet all 5 of the criteria listed below adopted by the BlueCross BlueShield Association Technology Evaluation Center (TEC) are deemed to be experimental/investigational:

1. The technology* must have final approval from the appropriate U.S. government regulatory bodies; and
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes; and
3. The technology must improve the net health outcome; and
4. The technology must be as beneficial as any established alternatives; and
5. The improvement must be attainable outside the investigational settings.

* Technology includes drugs, devices, processes, systems, or techniques

Rationale:

1. The technology must have final approval from the appropriate U.S. government regulatory bodies:

On June 7, 2021, the FDA approved Aduhelm (aducanumab) for the treatment of Alzheimer's disease. The approval was granted through the accelerated approval pathway. This program allows for earlier approval of drugs that treat serious conditions and that fill an unmet medical need based on a surrogate endpoint. A surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit but is not itself a measure of clinical benefit. On July 8, 2021, the approved indications for Aduhelm were updated to state "Treatment with ADUHELM 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."

2. The scientific evidence must permit conclusions concerning the effect on health outcomes:

In 2016 Biogen reported a phase 1b study with Aduhelm. The study included 164 mildly symptomatic Alzheimer's disease patients that were divided into four treatment groups: 1 mg/kg, 3 mg/kg, 6 mg/kg, or 10 mg/kg. Patients received one infusion per month for 12 months. Outcomes were level of Aβ detected by positron emission tomography (PET) and scores on the Clinical Dementia Rating – Sum of Boxes and Mini Mental State Examination. Researchers found that one year of monthly intravenous infusions of aducanumab reduces brain Aβ in a dose- and time-dependent manner. However, scores on the functional tests were less encouraging.

The encouraging results of the Sevigny et al., 2016 study were followed by two Phase 3 clinical studies conducted by Biogen. The trials, named EMERGE and ENGAGE, enrolled individuals with mild cognitive impairment (MCI) or mild dementia who had elevated Aβ as detected by PET imaging. The primary outcome for the studies was the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB). The reason for conducting two simultaneous studies was to demonstrate reproducibility of study results.

Amendments to the initial study protocol were made in March 2017 that increased the dose of Aduhelm for some study participants. Despite this change in dose, researchers proceeded to conduct a futility analysis at the initially planned timepoint. An interim analysis was conducted using a dataset from December 2018. In March 2019 Biogen issued a press release in which they stated the trials had been halted because the initial research outcome required that both trials had to demonstrate benefits from Aduhelm. The dataset used in the interim analysis showed that one of the studies met futility criteria (ENGAGE) while the other was trending positive (EMERGE). In other words, one study did not demonstrate a slowing of cognitive decline while the other study suggested a slowing of cognitive decline. Biogen explained the difference in results as possibly being attributed to the longer duration of exposure to a high dose of drug in the EMERGE study.

In October 2019 Biogen issued another press release in which they stated that analyses of subgroups within the study data revealed that beneficial effects of Aduhelm could be observed in both studies. The company proceeded to submit a New Drug Application to the FDA. The results of the trials were presented to the Peripheral and Central Nervous System Drugs Advisory Committee of the FDA in November who recommended the FDA not to approve the drug. The panel consisted of 11 experts – 10 voted no and 1 abstained. The committee concluded there was insufficient evidence supporting the effectiveness of aducanumab for the treatment of Alzheimer's disease.

Appropriate candidates for Aducanumab are identified using imaging and cognitive testing. A PET scan is needed to demonstrate amyloid plaques while cognitive office testing diagnoses MCI or early-stage dementia. Prior to the initial infusion of Aducanumab, a baseline MRI scan needs to be completed and then needs to be repeated prior to the 7th and 12th infusion. The infusion is given every 4 weeks. As part of the FDA label, it is stated *that Aduhelm can cause amyloid related imaging abnormalities-edema (ARIA-E), which can be observed on MRI as brain edema or sulcal effusions, and amyloid related imaging abnormalities hemosiderin deposition (ARIA-H), which includes microhemorrhage and superficial siderosis.* If there is an Aducanumab related imaging abnormality, then the drug is recommended to be stopped and the MRI is to be repeated prior to restarting. If the MRI shows improvement or is stable, then the drug may be restarted.

The Institute for Clinical and Economic Review has stated, "Given the certainty that harms can occur in patients treated with aducanumab and uncertainty about benefits, we rate the evidence to be insufficient to determine the net health benefit of aducanumab ("I") in patients with MCI and mild AD.*"* The ICER report states prior clinical trials of anti-amyloid drugs have suggested a lack of benefit among patients with moderate or severe Alzheimer's disease and this it is unlikely that aducanumab would benefit patients with moderate or severe Alzheimer's disease.

The American Geriatrics Society sent a letter to the FDA in which their concerns about approval of aducanumab were outlined. Those concerns included the incomplete status of the clinical trials of aducanumab, reliance on a

single, incomplete trial as the basis for approval, and the ambiguity regarding the clinical relevance of the findings from the incomplete trials. Additionally, the society noted a substantial incidence of adverse events were observed in the trial, the demographics of trial participants were unclear, and the post hoc analysis should have been used to generate more hypotheses rather than as a basis for FDA approval. The Society expressed that a lack of evidence exists to demonstrate the potential benefit of aducanumab outweighs the potential harms.

In conclusion, the scientific evidence does not permit conclusions concerning the effect on health outcomes.

3. **The technology must improve the net health outcome:**

   No studies have examined the impact of this technology on net health outcome.

4. **The technology must be as effective as any established alternatives:**

   This drug is the only drug to be approved for treating Alzheimer's disease in nearly 20 years. No established alternatives exist.

5. **The improvement must be attainable outside the investigational settings:**

   There is no evidence of improvement outside the investigational setting.
   This medication has not been available for clinical use outside the investigative setting. The medication was approved through the accelerated approval pathway. This means additional post-marketing studies are mandated, but those studies are not yet completed.

Update 2022:
A search of the peer-reviewed literature was performed from January 2022 through April 2022. Findings in the recent literature do not change the policy statement.

Benefit Applications

NOTE: For FEP business check the member's contract for benefits.

Provider Guidelines

There are no Provider Guidelines for this Medical Policy.

Cross References to Related Policies and Procedures

There are no Related Policies for this Medical Policy.

References

The following were among the resources reviewed and considered in developing this policy. By reviewing and considering the resources, CareFirst does not in any way endorse the contents thereof nor assume any liability or responsibility in connection therewith. The opinions and conclusions of the authors of these resources are their own and may or may not be in agreement with those of CareFirst.

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