Oscar Clinical Guideline: Aduhelm (aducanumab-avwa) (PG139 Ver. 1)

Aduhelm (aducanumab-avwa)

Summary

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the gradual decline of cognitive functions, including memory, thinking, and reasoning abilities. It is the most common cause of dementia in older adults, affecting millions of people worldwide. The disease primarily impacts individuals over 65 years of age, but early-onset Alzheimer's can occur in people as young as 40.

The exact cause of Alzheimer's is not entirely understood, but it is believed to involve a combination of genetic, environmental, and lifestyle factors. At the microscopic level, the disease is associated with the accumulation of amyloid-beta (Aβ) plaques and neurofibrillary tangles in the brain, leading to neuronal dysfunction and cell death.

Currently, there is no cure for Alzheimer's disease. Treatment primarily focuses on managing symptoms and improving the quality of life for patients. The available treatments can be divided into symptomatic treatments, disease-modifying therapies, and non-pharmacological interventions.

- Symptomatic treatments: These medications aim to alleviate cognitive and behavioral symptoms, such as memory loss and confusion. They include cholinesterase inhibitors (e.g., donepezil, rivastigmine, and galantamine) and the NMDA receptor antagonist memantine. These drugs can help manage symptoms, but they do not address the underlying disease progression.

- Disease-modifying therapies: Disease-modifying therapies aim to target the underlying pathophysiology of Alzheimer's disease, with the goal of slowing down or halting its progression. Two notable examples of these therapies include `BI™ (lecanemab-irmb) and ADUHELM® (aducanumab-avwa).
- Non-pharmacological interventions: A comprehensive approach to Alzheimer's disease treatment should not only focus on pharmacological options, such as symptomatic treatments and disease-modifying therapies, but also consider non-pharmacological interventions and caregiver support to provide the best possible care for patients and their families. Non-pharmacological interventions, including cognitive stimulation, physical activity, and social engagement, play a vital role in managing Alzheimer's disease and improving patients' quality of life. These interventions contribute to preserving cognitive function, postponing symptom progression, and adopting a more comprehensive approach to patient care.

ADUHELM® (aducanumab-avwa) is an amyloid beta-directed antibody indicated for the treatment of Alzheimer's disease. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with ADUHELM® (aducanumab-avwa). Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s). Despite its potential as a disease-modifying therapy, current evidence does not strongly support the use of ADUHELM® (aducanumab-avwa) for treating patients with early-stage Alzheimer's and mild cognitive impairment. The safety and efficacy of ADUHELM® (aducanumab-avwa) has not been established in these populations and further research is needed to determine its potential in these patient populations. Additionally, ADUHELM® (aducanumab-avwa) has been associated with side effects such as amyloid-related imaging abnormalities (ARIA) and the risk of ARIA should be carefully considered when using this medication.

Definitions

"ADAS-Cog (Alzheimer's Disease Assessment Scale - Cognitive Subscale)" is a widely used cognitive test specifically designed to evaluate the cognitive function of individuals with Alzheimer's disease. It assesses various cognitive domains, such as memory, language, praxis, and orientation. The ADAS-Cog has multiple versions with different numbers of items; the 14-item version is often used in clinical trials. Higher scores on the ADAS-Cog indicate greater cognitive impairment.

"ADCOMS (Alzheimer's Disease Composite Score)" is a composite score that combines selected items from the CDR-SB, MMSE, and ADAS-Cog to create a single measure of cognitive and functional performance in Alzheimer's disease. The ADCOMS has been developed specifically for use in clinical trials to detect treatment effects in the early stages of the disease.

"Alzheimer's disease (AD)" is a progressive neurodegenerative disorder characterized by a decline in cognitive functions, such as memory, thinking, and reasoning abilities. It is the most common cause of dementia in older adults.

"Amyloid-beta (Aβ) plaques" are abnormal protein deposits that accumulate in the brain and are associated with Alzheimer's disease. They consist of amyloid-beta peptides, which are thought to contribute to neuronal dysfunction and cell death.

"CDR-SB (Clinical Dementia Rating Scale Sum of Boxes)" is a widely used tool to assess the severity of dementia, particularly Alzheimer's disease. It measures cognitive and functional performance in six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Each domain is rated on a scale from 0 (no impairment) to 3 (severe impairment), resulting in a sum of boxes score ranging from 0 to 18, with higher scores indicating greater severity of dementia.

"Cholinesterase inhibitors" is a class of drugs used to treat Alzheimer's disease by increasing the levels of the neurotransmitter acetylcholine in the brain, which can help improve cognitive function. Examples include donepezil, rivastigmine, and galantamine.

"Dementia" is a general term for a decline in mental ability severe enough to interfere with daily life. It is not a specific disease but an overall term that describes a wide range of symptoms associated with a decline in memory or other thinking skills.

"Disease-modifying therapies" refer to treatments that aim to target the underlying pathophysiology of a disease, with the goal of slowing down or halting its progression.

"Experimental or Investigational" are terms used to describe treatments, procedures, or services that are not considered standard of care or have not been proven to be safe and effective for a specific condition. These treatments are generally not covered by the Plan.

"Futility" refers to the condition of being ineffective, producing no meaningful results, or being unable to achieve its intended purpose. In a clinical trial context, futility criteria refer to pre-determined guidelines or thresholds that are used to determine whether a study should be stopped early, usually due to a lack of efficacy or a low probability of obtaining meaningful results. In other words, futility criteria are used to assess whether a study is likely to fail to achieve its objectives or produce meaningful results, and to make the decision to stop the study early to avoid wasting resources and minimize the risk of exposing participants to ineffective treatments.

"MMSE (Mini-Mental State Examination)" is a brief, 30-point questionnaire that is used to assess cognitive function in older adults. It measures various cognitive domains, including orientation, registration, attention and calculation, recall, and language. The MMSE is scored from 0 to 30, with lower scores indicating more severe cognitive impairment.

"Neurofibrillary tangles" are abnormal accumulations of the protein tau inside brain cells that are also associated with Alzheimer's disease. These tangles disrupt the normal functioning of cells and are thought to contribute to cell death.

"NMDA receptor antagonist" is a type of drug that blocks the NMDA receptor, a protein involved in the communication between brain cells. Memantine is an NMDA receptor antagonist used to treat Alzheimer's disease.

"PET SUVR (Positron Emission Tomography Standardized Uptake Value Ratio)" is a quantitative measure used in amyloid PET imaging to assess the levels of amyloid-beta plaques in the brain. In the context of Alzheimer's disease, PET SUVR is used to determine the extent of amyloid-beta plaque accumulation in specific brain regions. Higher SUVR values indicate higher levels of amyloid-beta plaques, which are associated with Alzheimer's disease.

"Repeatable Battery for Assessment of Neuropsychological Status (RBANS)" is a neuropsychological test used to evaluate cognitive function in individuals. It assesses cognitive domains including immediate memory, visuospatial/constructional abilities, language, attention, and delayed memory. The RBANS is used to diagnose and track changes in cognitive function over time in individuals with neurocognitive disorders, including Alzheimer's disease and other forms of dementia.

"Symptomatic treatments" refers to medications that aim to alleviate the cognitive and behavioral symptoms of a disease, such as memory loss and confusion, without addressing the underlying disease progression.

Policy Statement on ADUHELM® (aducanumab-avwa) Efficacy Information

Considering the existing efficacy data, the Plan deems Aducanumab (Aduhelm; Biogen Inc.) for treating early-stage Alzheimer's disease patients with mild cognitive symptoms as experimental or investigational and not medically necessary. This stance is based on the current knowledge and available evidence regarding Aducanumab's efficacy, safety profile, and associated risks.

The FDA granted ADUHELM® (aducanumab-avwa) approval in a disputed decision after reanalyzed data from one of two terminated, identical phase III trials demonstrated a reduction in amyloid-beta within the brains of high-dose recipients, whereas no significant changes were observed in lower-dose or placebo patients (i.e., the sponsor ended both studies ahead of schedule due to predetermined interim criteria for futility). Nevertheless, this higher, recommended dose was linked to symptomatic and asymptomatic amyloid-related imaging abnormalities (ARIA) in up to 40% of patients. An examination of complete clinical study texts reveals little or unclear support for Aducanumab as a treatment for early-stage Alzheimer's disease patients with mild cognitive symptoms. Studies report a significant ARIA risk compared to placebo and no evident clinical benefits in patient-oriented outcomes.

Amyloid Related Imaging Abnormalities (ARIA)

ADUHELM® (aducanumab-avwa) can cause amyloid related imaging abnormalities (ARIA-E and ARIA-H), which can be observed as brain edema or sulcal effusions, microhemorrhage, and superficial siderosis on MRI. In clinical studies, 41% of patients treated with the 10 mg/kg dose of aducanumab experienced ARIA-E and/or ARIA-H compared to 10% of patients treated with placebo. ARIA-E was more likely to occur in ApoE ε4 carriers, and symptoms such as headache, confusion, dizziness, visual disturbance, and nausea were reported in 24% of patients treated with aducanumab 10 mg/kg and 5% of patients treated with placebo. Baseline brain MRI is recommended prior to starting aducanumab, and additional MRIs may be needed to evaluate for ARIA. Heightened clinical vigilance and careful evaluation is recommended if ARIA is observed on MRI, and temporary or permanent discontinuation of the drug may be required.

The approval of ADUHELM® (aducanumab-avwa) for Alzheimer's disease is based on two identically designed phase 3 clinical studies (Studies 301 and 302) in patients with confirmed presence of amyloid pathology and mild cognitive impairment or mild dementia consistent with stage 3 and 4 Alzheimer's disease. Patients included in these studies had a Mini-Mental State Examination (MMSE) score of 24–30, a Repeatable Battery for Assessment of Neuropsychological Status (RBANS) delayed memory index score ≤85, and a Clinical Dementia Rating-Sum of Boxes (CDR-SB) global score of 0.5. Both studies were double-blinded and placebo-controlled, with patients receiving low-dose or high-dose ADUHELM® (aducanumab-avwa) or placebo by IV infusion every 4 weeks for 18 months, followed by an optional long-term extension period.

- The results of Study 302 (EMERGE, NCT02484547) showed that high-dose ADUHELM® (aducanumab-avwa) reduced clinical decline compared to placebo, as measured by the change in CDR-SB score from baseline to week 78. Low-dose ADUHELM® (aducanumab-avwa) did not produce statistically significant effects when compared with placebo. Imaging results from a substudy found that the mean change from baseline to week 78 in brain amyloid beta PET composite was significantly reduced in the high-dose and low-dose groups compared to placebo, with greater efficacy noted in the high-dose group.
- Study 301 (ENGAGE, NCT02477800) showed no significant difference in the primary efficacy endpoint between ADUHELM® (aducanumab-avwa)-treated patients and placebo. Similar to Study 302, the mean change from baseline to week 78 in brain amyloid beta PET composite was significantly reduced in the high-dose and low-dose ADUHELM® (aducanumab-avwa) groups compared to placebo within the substudy.
- Results from a phase 1b dose-ranging study (Study 103; PRIME, NCT01677572) were also used to support the efficacy of ADUHELM® (aducanumab-avwa). The study enrolled a similar demographic of patients as Studies 301 and 302, with the mean change from baseline to week 54 in brain amyloid beta composite SUVR being significantly reduced in the ADUHELM® (aducanumab-avwa) 3-, 6-, and 10-mg/kg groups compared to placebo. However, this trial was designed to evaluate ADUHELM® (aducanumab-avwa) safety and the clinical assessments were only exploratory as the study was not sufficiently powered to detect clinical change.

A review of comprehensive clinical practice guidelines and position statements suggests that there is little support for using ADUHELM® (aducanumab-avwa) to treat patients with early-stage Alzheimer's disease and mild cognitive symptoms. In fact, most guidelines explicitly advise against its use or recommend its application only in a limited patient population or research setting.

Medical Necessity Criteria for ADUHELM® (aducanumab-avwa)

The Plan has not established medical necessity criteria for ADUHELM® (aducanumab-avwa) due to the inadequate evidence available to determine its clinically significant benefits for the treatment of Alzheimer's disease. As a result, the Plan cannot support or endorse the use of ADUHELM® (aducanumab-avwa) for the treatment of Alzheimer's disease at this time.

- Study 301 (PRIME) reported a positive outcome, showing that Aduhelm led to a significant reduction in amyloid beta plaques and a modest reduction in cognitive decline. However, study 302 (ENGAGE) failed to replicate these results, showing no significant difference in cognitive decline between the treatment and placebo groups.
- Both studies reported a high incidence of adverse events, including brain swelling (ARIA-E) and microhemorrhages. These safety concerns add to the uncertainty surrounding the drug's overall risk-benefit profile.
- In study 301, the positive effect observed was modest, with only a small difference in cognitive decline between the treatment and placebo groups. This raises questions about the clinical significance of the drug and whether the benefits outweigh the risks and costs associated with its use.
- After the termination of aducanumab's phase 3 studies, further analysis was conducted to determine the significance of the high-dose group's treatment effect compared to placebo in Study 302 and to identify reasons for the conflicting evidence of efficacy between the two studies. Despite post-hoc analyses, it was unclear why there were discrepant findings between Study 301 and 302, and the baseline demographics of the studies were unlikely to explain the differences in outcomes.
- While the Peripheral and Central Nervous System Drugs Advisory Committee voted that the evidence was insufficient to support the effectiveness of aducanumab for Alzheimer's disease, the FDA still approved the drug via the accelerated approval pathway. This pathway requires the use of a valid surrogate marker likely to predict clinical benefit, which, in this case, was the reduction of amyloid beta plaques. Although a reduction in amyloid beta plaques was observed with aducanumab, there has been controversy over the use of this surrogate marker as evidence of an improved clinical outcome. While the reduction of amyloid beta plaques was consistently demonstrated across trials, experts disagree on whether it is an appropriate surrogate endpoint, and several organizations and expert panels have published position statements expressing concerns over its use.

Experimental or Investigational / Not Medically Necessary

ADUHELM® (aducanumab-avwa) for any indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. This determination is based on the lack of sufficient clinical evidence demonstrating the efficacy and safety of ADUHELM® (aducanumab-avwa). Non-covered indications include, but are not limited to, the following:

- the treatment of Alzheimer's disease, including:
    - mild cognitive impairment or mild dementia stage of the disease.
    - moderate to severe Alzheimer's disease or other stages of dementia.
- Treatment of other neurodegenerative disorders or cognitive impairments unrelated to Alzheimer's disease.
- Prophylactic or preventive treatment in individuals without Alzheimer's disease or at risk for developing Alzheimer's disease.
- Use in combination with other experimental or investigational therapies for Alzheimer's disease or other cognitive disorders.

The Plan will continue to monitor the evidence and update the coverage policy as new information becomes available. In the meantime, we encourage healthcare providers and members to consider alternative treatment options with proven efficacy and established medical necessity criteria for the management of Alzheimer's disease and other cognitive disorders.

Applicable Billing Codes (HCPCS/CPT Codes)

CPT/HCPCS Codes considered experimental or investigational or not considered medically necessary:	
Code	*Description*
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96366	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)
C9399	Unclassified drugs or biologicals
J3590	Unclassified biologics
J0172	Injection, aducanumab-avwa, 2 mg
ICD-10 Codes considered experimental or investigational or not considered medically necessary:	
Code	*Description*

G30	Alzheimer's disease
G30.0	Alzheimer's disease with early onset
G30.1	Alzheimer's disease with late onset
G30.8	Other Alzheimer's disease
G30.9	Alzheimer's disease, unspecified
F00	Dementia in Alzheimer's disease
F00.0	Dementia in Alzheimer's disease with early onset
F00.1	Dementia in Alzheimer's disease with late onset
F00.2	Dementia in Alzheimer's disease, atypical or mixed type
F00.9	Dementia in Alzheimer's disease, unspecified
F01	Vascular dementia
F01.50	Vascular dementia without behavioral disturbance
F01.51	Vascular dementia with behavioral disturbance
F02	Dementia in other diseases classified elsewhere
F02.80	Dementia in other diseases classified elsewhere without behavioral disturbance
F02.81	Dementia in other diseases classified elsewhere with behavioral disturbance
F03	Unspecified dementia
F03.90	Unspecified dementia without behavioral disturbance
F03.91	Unspecified dementia with behavioral disturbance
F05	Delirium due to known physiological condition

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