

Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer’s Disease

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[➔ Instructions for Use](#)

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Commercial Policy
<ul style="list-style-type: none"> Aduhelm® (Aducanumab-Avwa)

Application

This Medical Benefit Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy/Guideline
Arizona	Refer to the state’s Medicaid clinical policy
Florida	Refer to the state’s Medicaid clinical policy
Indiana	Refer to the state’s Medicaid clinical policy
Kansas	Refer to the state’s Medicaid clinical policy
North Carolina	None
Ohio	None
Pennsylvania	Refer to the state’s Medicaid clinical policy
Texas	Refer to drug-specific criteria found within the Texas Medicaid Provider Procedures Manual

For the following states, this Medical Benefit Drug Policy doesn’t apply in certain circumstances:

State	Policy/Guideline
Kentucky	For Aduhelm : Refer to the state’s Medicaid clinical policy
Louisiana	For Aduhelm : Refer to the state’s Medicaid clinical policy For Leqembi : Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer’s Disease (for Louisiana Only)
Minnesota	For Aduhelm : Refer to the state’s Medicaid clinical policy
Mississippi	For Aduhelm : Refer to the state’s Medicaid clinical policy

Coverage Rationale

Leqembi (lecanemab-irmb) may be covered for the treatment of Alzheimer's disease (AD) in patients who meet all of the following criteria:

- For **initial therapy**, all of the following:
 - Diagnosis of **one** of the following based on National Institute on Aging and the Alzheimer's Association (NIA-AA) criteria^{22,55}:
 - Mild cognitive impairment (MCI) due to Alzheimer's disease; **or**
 - Probable Alzheimer's disease dementia;**and**
 - Submission of medical records (e.g., chart notes, laboratory values) documenting **all** of the following^{53,56}:
 - Global Clinical Dementia Rating (CDR) score of 0.5 or 1.0; **and**
 - CDR Memory Box score of 0.5 or greater; **and**
 - **One** of the following:
 - Mini-Mental State Examination (MMSE) score of 22 or greater
 - Saint Louis University Mental Status (SLUMS) score of 17 or greater
 - Montreal Cognitive Assessment (MoCA) score of 17 or greater**and**
 - Submission of medical records (e.g., chart notes, laboratory values) documenting the presence of beta-amyloid protein deposition, as evidenced by **one** of the following:
 - Positive amyloid positron emission tomography (PET) scan; **or**
 - **Both** of the following:
 - Attestation that the patient does not have access to amyloid PET scanning; **and**
 - Cerebrospinal fluid (CSF) biomarker testing documents abnormalities suggestive of beta-amyloid accumulation in the brain (e.g., A β 42: 40 ratio, p-tau/A β 42);**and**
 - Other differential diagnoses [e.g., dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), vascular dementia, pseudodementia due to mood disorder, vitamin B12 deficiency, encephalopathy, etc.] have been ruled out; **and**
 - **One** of the following:
 - Patient is not currently taking an anticoagulant (e.g., warfarin, dabigatran); **or**
 - **Both** of the following^{53,55,56}:
 - Patient is currently taking an anticoagulant (e.g., warfarin, dabigatran); **and**
 - Counseling has been provided that the combined use of Leqembi with anti-coagulant drugs may increase the risk of cerebral macrohemorrhage and prescriber attests that the patient has shared in decision-making to initiate Leqembi therapy;**and**
 - Patient has no history of intracerebral hemorrhage [e.g., transient ischemic attack (TIA), stroke] within the previous year prior to initiating treatment; **and**
 - Counseling has been provided on the risk of amyloid-related imaging abnormalities (ARIA-E and ARIA-H) and patient is aware to monitor for headache, dizziness, visual disturbances, nausea, and vomiting; **and**
 - **All** of the following:
 - Counseling has been provided on how testing for ApoE ϵ 4 status informs the risk of developing ARIA when deciding to initiate treatment with Leqembi; **and**
 - Testing for ApoE ϵ 4 status has been offered to the patient and prescriber attests that the patient has shared in decision-making to initiate Leqembi therapy;**and**
 - A baseline brain magnetic resonance imaging (MRI) has been completed within 12 months prior to initiating treatment; **and**
 - Not used in combination with other A β monoclonal antibodies (mAbs) for Alzheimer's Disease (e.g., Aduhelm); **and**
 - Prescribed by a neurologist, geriatric psychiatrist, or geriatrician who specializes in treating dementia; **and**
 - Prescriber attests that the prescriber's site is currently registered or will seek registration with the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) or other comparable patient registry that collects information on treatments

- for Alzheimer’s disease, including Leqembi; **and**
- Leqembi dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
- Initial authorization will be for no more than 6 months
- For **continuation of therapy**, **all** of the following:
 - Patient continues to have one of following diagnoses based on National Institute on Aging and the Alzheimer’s Association (NIA-AA) criteria^{22,55}:
 - Mild cognitive impairment (MCI) due to Alzheimer’s disease; **or**
 - Probable Alzheimer’s disease dementia;
 - and**
 - Submission of current medical records (e.g., chart notes, laboratory values) documenting that the patient continues to meet **all** of the following (updated assessments must be measured no earlier than 4 weeks prior to a continuation request)^{53,56}:
 - Global Clinical Dementia Rating (CDR) score of 0.5 or 1.0; **and**
 - CDR Memory Box score of 0.5 or greater; **and**
 - **One** of the following:
 - Mini-Mental State Examination (MMSE) score of 22 or greater
 - Saint Louis University Mental Status (SLUMS) score of 17 or greater
 - Montreal Cognitive Assessment (MoCA) score of 17 or greater
 - and**
 - Both of the following:
 - Submission of medical records (e.g., chart notes) confirming follow-up brain magnetic resonance imaging (MRI) has been completed after the initiation of therapy and prior to the 5th and 7th infusion treatment; **and**
 - **One** of the following:
 - ARIA has not been observed on MRI; **or**
 - **All** of the following:
 - ARIA has been observed on MRI; **and**
 - Prescriber attests that continuation of therapy with Leqembi is appropriate based on the severity of the patient’s clinical symptoms; **and**
 - **One** of the following:
 - Follow-up MRI demonstrates radiographic resolution and/or stabilization; **or**
 - Prescriber attests that continuation of therapy with Leqembi is appropriate based on the radiographic severity of ARIA;
 - and**
 - Not used in combination with other A β monoclonal antibodies (mAbs) for Alzheimer’s Disease (e.g., Aduhelm); **and**
 - Prescribed by a neurologist, geriatric psychiatrist, or geriatrician who specializes in treating dementia; **and**
 - Leqembi dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
 - Reauthorization is for no more than 6 months

Leqembi (lecanemab-irmb) is unproven and not medically necessary for any indication other than mild cognitive impairment due to Alzheimer’s disease and mild Alzheimer’s disease dementia.

Aduhelm (aducanumab-awwa) is covered for the treatment of Alzheimer’s disease (AD) when all of the following criteria are met*:

- Diagnosis of mild cognitive impairment (MCI) due to AD or mild AD dementia; **and**
- Patient has confirmed presence of amyloid beta pathology consistent with AD; **and**
- Consistent with the Centers for Medicare & Medicaid Services (CMS) decision memo [CMS Final Decision Memo – *Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer’s Disease (CAG-00460M)*] the patient will be receiving Aduhelm through an FDA randomized controlled trial conducted under an investigational new drug (IND) application⁵¹

*The Centers for Medicare & Medicaid Services (CMS) covers Food and Drug Administration (FDA) approved monoclonal antibodies directed against amyloid for the treatment of Alzheimer’s disease (AD) when furnished under coverage with evidence development (CED). Approved CED studies are posted on the CMS Coverage with Evidence Development webpage (refer to: [Coverage with Evidence Development | CMS](#)).

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J0172	Injection, aducanumab-awwa, 2 mg
J0174	Injection, lecanemab-irmb, 1 mg

Diagnosis Code	Description
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

Background

Alzheimer's disease (AD) is the most common cause of dementia and accounts for an estimated 60% to 80% of cases¹. After AD, the most common neurodegenerative dementias are Lewy body disease, characterized by chronic rapid eye movement (REM) sleep behavior disorder, early visuospatial impairment, and parkinsonism; and frontotemporal dementia, characterized by a behavioral variant or less often, a language impairment variant.²

AD is characterized by deposition of A β plaques and neurofibrillary tangles (comprised of abnormal tau protein) in the brain, accompanied by synaptic dysfunction and neurodegeneration.^{3,4} The deposition of A β (as amyloid plaques) generally begins decades before any symptoms of AD are observed. More specifically, A β deposition is followed sequentially by markers of neurodegeneration, accumulation of tau pathology, and brain volume loss. This pre-symptomatic phase of AD will precede the emergence of AD symptoms 10 to 20 years prior.⁵

Tau is the microtubule associated protein (MAP) of a normal mature neuron. Tau is a phosphoprotein that promotes the assembly of tubulin into microtubules and stabilization of their structure. In AD (and certain other related neurodegenerative diseases, called tauopathies), tau protein is abnormally hyperphosphorylated and aggregated into bundles of filaments. In AD, this tau pathology is seen as intraneuronal neurofibrillary tangles of paired helical filaments sometimes admixed with straight filaments. Aggregates of abnormally hyperphosphorylated filaments are also seen in dystrophic neurites surrounding the A β plaque core, and in the neuropil as neuropil threads.⁶

There are 2 ways to detect abnormal A β , either directly via PET imaging using tracers or indirectly by measuring the levels of the long form of A β in the CSF. P-tau and t-tau can also be detected using CSF and are used as biomarkers to detect the emergence of AD in patients with MCI.⁷

Age of AD onset:⁸

- Typical AD: AD is characteristically a disease of older age. The incidence and prevalence of AD increase exponentially with age, essentially doubling in prevalence every 5 years after the age of 65 years.
- Early-onset dementia: Although less common, early-onset dementia occurs in patients < 65 years of age. These patients often present with symptoms somewhat atypical for this disease, such as language, visual, or mood-behavioral changes rather than predominant memory loss. A study from the United Kingdom estimated that the incidence of dementia in individuals 30 to 65 years of age was approximately 54 per 100,000 person-years. The most common cause of dementia in these patients was AD (34%), followed by vascular dementia (18%), frontotemporal dementia (12%), dementia with Lewy bodies (7%), and alcohol-related dementia (10%)⁹.

- Inherited forms of AD: These forms of AD are rare (< 1% of all AD cases) and routinely present before 65 years of age, frequently in the fifth decade or earlier. Inherited forms of AD typically exhibit an autosomal-dominant inheritance pattern related to mutations in genes that alter A β protein production or metabolism, including amyloid precursor protein (APP), presenilin-1 (PSEN1), and presenilin-2 (PSEN2).
- AD associated with Down syndrome: Patients with Down syndrome have an additional gene dose of APP due to trisomy of chromosome 21 and inevitably develop AD pathology. Symptoms tend to emerge at an earlier age, i.e., 10 to 20 years earlier than the general population with AD.

Risk factors for AD:²

- Aging is an important risk factor for dementia. AD affects 5% to 10% of people > 65 years of age, and 50% of those \geq 85 years of age.
- Nonmodifiable risk factors for AD include female gender, Black race, Hispanic ethnicity, and genetic factors such as presence of the APOE gene.
- Modifiable risk factors for all-cause dementia include hypertension, diabetes, diet, and limited cognitive, physical, and social activities.

While the genetic basis for early-onset AD is much better understood, the genetic basis of late-onset AD is considered far more complex, with susceptibility conferred by a variety of more common but less penetrant genetic factors likely interacting with environmental and epigenetic influences. To date, the most firmly established genetic risk factor for late-onset disease is APOE:¹⁰

- The APOE gene is located on chromosome 19 and exists in 3 alleles: epsilon 2, 3, and 4. The APOE epsilon 4 (ϵ 4) allele has been confirmed to be an important risk factor for AD in many clinical trials.
- Factors that may influence the impact of APOE ϵ 4 on AD risk include female gender, African/African-American race (although there are conflicting data), vascular risk factors (e.g., smoking, diabetes, hypertension, and hypercholesterolemia), and modifier genes/environment.
- Genetic testing is available for the known causative genes in early-onset AD but has not been widely adopted, likely in part because of the current lack of highly effective preventive or therapeutic strategies.

The symptoms at early stage AD are less pronounced than in later stages of AD, and therefore require measures that are different from those used in later stages.

The Clinical Dementia Rating – Sum of Boxes (CDR-SB) is an integrated scale that assesses both daily function and cognitive effects and was shown to be sufficiently sensitive and specific to detect change over time in early symptomatic AD patients. The scale integrates assessments from 3 domains of cognition (memory, orientation, judgment/problem-solving) and 3 domains of function (community affairs, home/hobbies, personal care). CDR-SB scores range from 0-18, with higher scores indicating greater disease severity. A minimal clinically important difference in CDR-SB has not been clearly defined but has been estimated to be 1-2 points.^{5,11,41} A CDR-SB score ranging from 0.5-4.0 has been reported to correspond to a CDR-G score of 0.5. A CDR-SB score ranging from 4.5-9.0 has been reported to correspond to a CDR-G score of 1.²⁶

CDR-SB Score	Disease Severity
0	Normal
0.5–4.0	Suggests questionable cognitive impairment to very mild dementia
0.5–2.5	Suggests questionable cognitive impairment
3.0–4.0	Suggests very mild dementia
4.5–9.0	Suggests mild dementia
9.5–15.5	Suggests moderate dementia
16.0–18.0	Suggests severe dementia

The Mini-Mental State Exam (MMSE) is a widely used performance-based test of global cognitive status. The MMSE is a measure of cognition that includes 11 tasks relating to topics of word recall, attention and calculation, language ability, and visuospatial function. The scale ranges from 0 to 30 with a lower score reflecting greater cognitive impairment. It has several known limitations impacting sensitivity to change, particularly in earlier disease stages: substantial ceiling effects, sensitivity to

practice effects, scores are impacted by patients' educational achievement, and learning effects are observed. The minimal clinically important difference of the MMSE in AD is estimated to be 1-3 points, and in early AD to be 1-2 points.^{5,11,12,27,41}

MMSE Score	Disease Severity
25–30	Normal to questionable cognitive impairment
19–24	Suggests mild dementia
10–18	Suggests moderate dementia
0–9	Suggests severe dementia

The Alzheimer's Disease Assessment Scale – Cognitive Subscale (13-Item version) (ADAS-Cog13) comprises both cognitive tasks and clinical ratings of cognitive performance. The scale items capture word recall, ability to follow commands, the ability to correctly copy or draw an image, naming, the ability to interact with everyday objects, orientation, word recognition, memory, comprehension of spoken language, word-finding, and language ability, with a measure for delayed word recall and concentration/distractibility. The total score ranges from 0 to 85 with an increase in score over time indicates increasing cognitive impairment. The minimal clinically important difference of the ADAS-COG 13 in early AD is estimated to be 3 points.^{5,11,42}

The Montreal Cognitive Assessment (MoCA) is a widely used screening test specifically designed to detect more subtle cognitive deficits that characterize mild cognitive impairment. Like the MMSE, the MoCA is scored on a 30-point scale, with items that assess delayed word recall, visuospatial/executive function, language, attention/concentration, and orientation. Studies examining head-to-head performance of patients on the MMSE and MoCA have shown that the MoCA is more difficult; MoCA scores are consistently lower than those obtained on the MMSE. The MoCA appears to be more sensitive than the MMSE for detecting MCI, though perhaps slightly less specific. A minimum clinically important difference of the MoCA in AD has not been described.⁴³

Assessment Scale	Minimal Clinical Important Difference
Clinical Dementia Rating-Sum of Boxes (CDR-SB)	1-2 points
Mini-Mental State Exam (MMSE)	1-3 points
Alzheimer's Disease Assessment Scale – Cognitive Subscale (13-Item version) (ADAS-Cog13)	3 points

The stages of AD dementia can be defined by the MMSE and MoCA scores below:¹²

- Mild dementia (MMSE 19 to 26; MoCA 12 to 16)
- Moderate dementia (MMSE 10 to 18; MoCA 4 to 11)
- Severe dementia (MMSE < 10; MoCA < 4)

The National Institute on Aging and the Alzheimer's Association (NIA-AA) research framework committee created a numeric clinical staging scheme (table below) applicable for diagnosing those in the Alzheimer's continuum. This staging scheme reflects the sequential evolution of AD from an initial stage characterized by the appearance of abnormal AD biomarkers in asymptomatic individuals. As biomarker abnormalities progress, the earliest subtle symptoms become detectable.⁴⁰

Stage	Numeric Clinical Staging – Applicable Only to Individuals in the Alzheimer's Continuum
Stage 1	<ul style="list-style-type: none"> • Performance within expected range on objective cognitive tests. Cognitive test performance may be compared to normative data of the investigator's choice, with or without adjustment (the choice of the investigators) for age, sex, education, etc.* • Does not report recent decline in cognition or new onset of neurobehavioral symptoms of concern • No evidence of recent cognitive decline or new neurobehavioral symptoms by report of an observer (e.g., study partner) or by longitudinal cognitive testing if available

Stage	Numeric Clinical Staging – Applicable Only to Individuals in the Alzheimer’s Continuum
Stage 2	<ul style="list-style-type: none"> • Normal performance within expected range on objective cognitive tests • Transitional cognitive decline: Decline in previous level of cognitive function, which may involve any cognitive domain(s) (i.e., not exclusively memory) • May be documented through subjective report of cognitive decline that is of concern to the participant • Represents a change from individual baseline within past 1–3 years, and persistent for at least 6 months • May be corroborated by informant but not required • Or may be documented by evidence of subtle decline on longitudinal cognitive testing but not required • Or may be documented by both subjective report of decline and objective evidence on longitudinal testing • Although cognition is the core feature, mild neurobehavioral changes – for example, changes in mood, anxiety, or motivation – may coexist. In some individuals, the primary complaint may be neurobehavioral rather than cognitive. Neurobehavioral symptoms should have a clearly defined recent onset, which persists and cannot be explained by life events[†] • No functional impact on daily life activities
Stage 3	<ul style="list-style-type: none"> • Performance in the impaired/abnormal range on objective cognitive tests • Evidence of decline from baseline, documented by the individual’s report or by observer (e.g., study partner) report or by change on longitudinal cognitive testing or neurobehavioral behavioral assessments • May be characterized by cognitive presentations that are not primarily amnesic[‡] • Performs daily life activities independently, but cognitive difficulty may result in detectable but mild functional impact on the more complex activities of daily life, that is, may take more time or be less efficient but still can complete, either self-reported or corroborated by a study partner
Stage 4	<ul style="list-style-type: none"> • Mild dementia • Substantial progressive cognitive impairment affecting several domains, and/or neurobehavioral disturbance. Documented by the individual’s report or by observer (e.g., study partner) report or by change on longitudinal cognitive testing • Clearly evident functional impact on daily life, affecting mainly instrumental activities. No longer fully independent/requires occasional assistance with daily life activities
Stage 5	<ul style="list-style-type: none"> • Moderate dementia • Progressive cognitive impairment or neurobehavioral changes. Extensive functional impact on daily life with impairment in basic activities. No longer independent and requires frequent assistance with daily life activities
Stage 6	<ul style="list-style-type: none"> • Severe dementia • Progressive cognitive impairment or neurobehavioral changes. 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
Notes	<p>* For stages 1-6: Cognitive test performance may be compared to normative data of the investigator’s choice, with or without adjustment (choice of the investigators) for age, sex, education, etc.</p> <p>[†] For stages 2-6: Although cognition is the core feature, neurobehavioral changes – for example, changes in mood, anxiety, or motivation – may coexist</p> <p>[‡] For stages 3-6: Cognitive impairment may be characterized by presentations that are not primarily amnesic</p>

Despite the existence of several FDA-approved therapies for AD, there is an unmet medical need for treatments that are intended to address the biological basis of AD. Currently approved treatments do not target the underlying pathology of AD.⁵ Cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) and the NMDA-antagonist, memantine, are the only FDA-approved and guideline-recommended treatments for AD dementia.¹³ The majority of patients with newly diagnosed AD should be offered a trial of a cholinesterase inhibitor for symptomatic treatment of cognition and global functioning. However, the degree of expected benefit is modest, and therapy should only be continued in patients who appear to be benefiting.¹²

Aducanumab is a human immunoglobulin gamma 1 (IgG1) monoclonal antibody that selectively targets aggregated forms of A β , including soluble oligomers and insoluble fibrils. Aducanumab crosses the blood-brain barrier and targets aggregated forms of A β in brain tissue, ultimately leading to clearance of A β plaques through a microglia-mediated phagocytosis process.^{4,7}

Leqembi (lecanemab-irmb) is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta. The accumulation of amyloid beta plaques in the brain is a defining pathophysiological feature of Alzheimer's disease.^{54,55}

Clinical Evidence

Multiple investigational anti-A β antibodies have been developed with the goal of either reducing production of A β or lowering levels of aggregated A β present in the brain, the latter of which has been the most pursued approach. Many of these investigational drugs have failed to demonstrate efficacy and/or safety. Some explanations for the failures of previous anti-A β antibodies include the following:^{5,14}

- Inclusion of patients in clinical trials without evidence of A β pathology
- Unknown or no target engagement prior to initiation of phase 3 study (i.e., poor selectivity of drug for neurotoxic A β)
- Lack of robust and sustained inhibition of soluble A β oligomers
- Use of subtherapeutic doses (possibly due to decreased brain penetration)
- Inclusion of patients at later stages of AD dementia, when significant irreversible neurodegeneration has already occurred

Aducanumab is the first anti-A β antibody to achieve proof of concept prior to phase 3 studies.⁵ After the completion of PRIME (Study 103; n = 165), which demonstrated a dose-dependent effect with aducanumab, 2 identically designed studies [ENGAGE (Study 301) and EMERGE (Study 302)] were initiated. Both studies were phase 3, double-blind, placebo-controlled, multicenter (global), randomized controlled trials (ENGAGE, n = 1,647; EMERGE, n = 1,638) and were designed to have a titration period of 6 months (to minimize risk of Aes), followed by administration of 14 doses of aducanumab over 12 months. Key inclusion criteria included patients age 50 to 85 years, a positive amyloid PET scan, a Clinical Dementia Rating Global (CDR-G) score of 0.5, a Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) score of \leq 85, a Mini-Mental State Exam (MMSE) score of \geq 24. Key exclusion criteria included a transient ischemic attack or stroke or any unexplained loss of consciousness within 1 year prior to screening, baseline MRI showing signs of previous hemorrhage, the history of a bleeding disorder, or the use of an antiplatelet or anticoagulant (aspirin at a dose of \leq 325 mg was allowed).

A total of 6,757 patients were screened for entry into the EMERGE study and 1,638 (24%) patients were randomized. The most common reasons reported for screening failure were having a specific AD functional score (CDR, MMSE or RBANS) outside the allowed range (62%) or not having a positive amyloid PET scan (16%). A total of 6,173 patients were screened for entry into the ENGAGE study and 1,647 (27%) patients were randomized. The most common reasons reported for screening failure were having a specific AD functional score (CDR, MMSE, or RBANS) outside the allowed range (67%) or not having a positive amyloid PET scan (12%). Patients were randomized 1:1:1 to the low-dose aducanumab, high-dose aducanumab, or placebo group, and stratified based on apolipoprotein E (APOE) ϵ 4 carrier status. A protocol amendment (protocol 4) eventually allowed for all patients in the high-dose aducanumab group to receive the 10 mg/kg target dose (previously only non-carriers of APOE ϵ 4 received this target dose). At baseline, 80% of patients were diagnosed with mild cognitive impairment (MCI) with 20% having mild AD; patients had a mean age of 70 and a mean score on the CDR-SB of 2.4.^{5,7}

In March 2019, Biogen conducted a prespecified interim futility analysis on pooled data from ENGAGE and EMERGE studies. Results of this futility analysis demonstrated that aducanumab failed to meet its objectives, which resulted in Biogen terminating phase 3 clinical trials. Subsequent examination of individual study results that included additional data that accrued during the time of the futility analysis revealed findings that differed from the results of the prespecified futility analysis. Most notably, statistically significant results were observed from EMERGE.^{5,15}

In the EMERGE study, high-dose aducanumab demonstrated statistically significant treatment effect on change from baseline in CDR-SB compared to placebo [-0.39, (95% CI -0.69 to -0.09), p = 0.012]. Statistically significant differences from placebo were also demonstrated in secondary endpoints of Mini Mental State Examination (MMSE), Alzheimer's Disease Cooperative Study Group – Activities of Daily Living (ADCS-ADL-MCI), and Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog13). In an exploratory analysis, statistically significant reductions in amyloid beta examined by PET were demonstrated in

the subset of evaluated patients treated with aducanumab at week 26 and 28. However, additional studies are needed to establish a clinical benefit.

The ENGAGE study, in contrast, failed to meet its primary and secondary endpoints at both low- and high-dose aducanumab. Consistent with the EMERGE study finding, statistically significant reductions in amyloid beta examined by PET were demonstrated in the subset of evaluated patients treated with aducanumab at week 26 and 28. A post-hoc analyses was conducted to understand why EMERGE demonstrated statistically significant outcomes while ENGAGE did not demonstrate benefit. Biogen concluded the following:

- A smaller subset of patients received the target dose of 10 mg/kg (due to the protocol amendment that occurred later in the study) in ENGAGE
- Based on their post-hoc analysis [using an extra 3 months of data (December 2018 to March 2019)], patients who did receive a sufficient number of aducanumab 10 mg/kg doses did demonstrate statistically significant results in this study
- There were a greater number of rapidly progressing AD patients in the high-dose group of the ENGAGE study, which could have contributed to the lack of benefit

Both the ENGAGE and EMERGE studies demonstrated safety concerns with the development of amyloid related imaging abnormalities (ARIA) in patients treated with aducanumab. ARIA can be classified as ARIA-E, ARIA with associated brain edema or sulcal effusions, or ARIA-H, ARIA which includes microhemorrhage and superficial siderosis. Of the patients who received high dose aducanumab, 41% experienced ARIA in ENGAGE and EMERGE. ARIA-E occurred in 35.0% and ARIA-H was observed in 28.3% in the high-dose arm across the two trials, compared with only 2.7% and 8.7% in the placebo arms, respectively. The risk of ARIA was greater in patients receiving aducanumab who were APOE ϵ 4 carriers compared to noncarriers. ARIA led to discontinuation of study therapy in 7% of participants receiving the high dose of aducanumab compared with only 0.6% of participants in the placebo arm. Due to these findings, aducanumab has a labeled warning for ARIA. A baseline MRI is required prior to initiating aducanumab and follow-up MRIs are also required prior to the 7th and 12th infusions of aducanumab to monitor for ARIA.

On November 6, 2020, the FDA PCNS advisory committee convened to examine data supporting the approval of aducanumab for AD. The advisory committee voted to not approve aducanumab. Key questions and corresponding responses are listed below:¹⁶

- “Does Study 302 (EMERGE), viewed independently and without regard for Study 301 (ENGAGE), provide strong evidence that supports the effectiveness of aducanumab for the treatment of AD?” Responses: 1 voted yes, 8 voted no, and 2 were uncertain
- “Has the Applicant presented strong evidence of a pharmacodynamic effect of aducanumab on AD pathophysiology?” Responses: 0 voted yes, 7 voted no, and 4 were uncertain
- “Does Study 103 (PRIME) provide supportive evidence of the effectiveness of aducanumab for the treatment of AD?” Responses: 5 voted yes, 0 voted no, and 6 were uncertain
- “In light of the understanding provided by the exploratory analyses of Study 301 and Study 302, along with the results of Study 103 and evidence of a pharmacodynamic effect on AD pathophysiology, is it reasonable to consider Study 302 as primary evidence of effectiveness of aducanumab for the treatment of AD?” Responses: 0 voted yes, 10 voted no, and 1 was uncertain

In March 2020, a global, OL, single-arm, phase 3b clinical trial [EMBARK (NCT04241068)] in approximately 2,400 patients was initiated with the primary objective of assessing the long-term safety of aducanumab 10 mg/kg in AD patients who were actively participating in aducanumab clinical trials [PRIME (phase 1b), EVOLVE (phase 2), ENGAGE (phase 3), and EMERGE (phase 3)] at the time of their early termination (March 2019).^{17,18} Secondary study objectives include long-term efficacy, and long-term effect of aducanumab on biomarkers and pharmacokinetic endpoints. Another goal of EMBARK is to provide answers regarding the effect of prolonged treatment interruption and improve understanding of the durability of aducanumab’s treatment effects.

FDA approval for lecanemab was based on Study 201, an 18-month, phase 2b, double-blind, placebo controlled, multicenter, randomized control trial that evaluated the safety and efficacy of lecanemab. The study aimed to establish the effective dose 90% (ED90), defined as the simplest dose that achieves $\geq 90\%$ of the maximum treatment effect. The primary endpoint was Bayesian analysis of 12-month clinical change on the Alzheimer’s Disease Composite Score (ADCOMS) for the ED90 dose, which required an 80% probability of $\geq 25\%$ clinical reduction in decline versus placebo. Study 201 enrolled 854 were treated to lecanemab, 609 or placebo, 245. Of the total number of patients randomized, 71.4% were ApoE ϵ 4 carriers and 28.6% were

ApoE ϵ 4 non-carriers. During the study, the protocol was amended to no longer randomize ApoE ϵ 4 carriers to the 10 mg/kg every two weeks dose arm. ApoE ϵ 4 carriers who had been receiving lecanemab 10 mg/kg every two weeks for 6 months or less were discontinued from study drug. The primary analysis conducted at Month 12 of treatment indicated that the 10 mg/kg IV biweekly dose (the effective dose) had a 64% probability to be better than placebo by 25% on ADCOMS at 12 months, missing the prespecified 80% probability threshold for the primary outcome.

The results for the Bayesian analysis for reduction of clinical decline at 18 months vs. placebo for 10 mg/kg biweekly on ADCOMS (-27%, with 97.7% probability to be superior to placebo), CDR-SB (33%, with 96.4% probability to be superior to placebo), and ADASCog14 (56%, with a 98.8% probability to be superior to placebo) were similar to the results from the corresponding conventional analyses for clinical measures when comparing mean change from baseline and least squares (LS) mean data.⁵⁴

The CLARITY AD phase 3 study was conducted to evaluate the efficacy of lecanemab in participants with early Alzheimer's disease (EAD) by determining the superiority of lecanemab compared with placebo on the change from baseline in the Clinical Dementia Rating – Sum of Boxes (CDR-SB) at 18 months of treatment in the Core Study.⁵¹ This study will also evaluate the long-term safety and tolerability of lecanemab in participants with EAD in the Extension Phase and whether the long-term effects of lecanemab as measured by the CDR-SB at the end of the Core Study is maintained over time in the Extension Phase. CLARITY AD was an 18-month, multicenter, double-blind, phase 3 trial involving persons 50 to 90 years of age with early Alzheimer's disease (mild cognitive impairment or mild dementia due to Alzheimer's disease) with evidence of amyloid on positron-emission tomography (PET) or by cerebrospinal fluid testing. 52 participants were randomly assigned in a 1:1 ratio to receive intravenous lecanemab (10 mg per kilogram of body weight every 2 weeks) or placebo. The primary end point was the change from baseline at 18 months in the score on the Clinical Dementia Rating – Sum of Boxes (CDR-SB; range, 0 to 18, with higher scores indicating greater impairment). Key secondary end points were the change in amyloid burden on PET, the score on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog14; range, 0 to 90; higher scores indicate greater impairment), the Alzheimer's Disease Composite Score (ADCOMS; range, 0 to 1.97; higher scores indicate greater impairment), and the score on the Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale for Mild Cognitive Impairment (ADCSMCI-ADL; range, 0 to 53; lower scores indicate greater impairment). A total of 1,795 participants were enrolled, with 898 assigned to receive lecanemab and 897 to receive placebo. The mean CDR-SB score at baseline was approximately 3.2 in both groups. The adjusted least-squares mean change from baseline at 18 months was 1.21 with lecanemab and 1.66 with placebo [difference, -0.45; 95% confidence interval (CI), -0.67 to -0.23; $p < 0.001$]. Furthermore, a slope analysis demonstrated that lecanemab took 5.5 to 6 months more time to achieve the same CDR-SB as placebo at 18 months, indicating a 5.5 to 6 month slowing of progression. A β plaque reduction was a secondary endpoint and was studied in a subset of patients ($n = 698$). The adjusted mean change from baseline at 18 months was -55.48 centiloids in the lecanemab group vs. 3.64 centiloids in the placebo group (adjusted mean difference, -59.12 centiloids; 95% CI, -62.64 to -55.60; $p < 0.001$). Lecanemab resulted in infusion-related reactions in 26.4% of the participants and amyloid-related imaging abnormalities with edema or effusions in 12.6%.⁵⁵

The incidence of ARIA-E with lecanemab was 12.5% vs. 1.7% with placebo (symptomatic ARIA-E: 2.8% vs. 0% with placebo). In a substudy involving 698 participants, there were greater reductions in brain amyloid burden with lecanemab than with placebo (difference, -59.1 centiloids; 95% CI, -62.6 to -55.6). Other mean differences between the two groups in the change from baseline favoring lecanemab were as follows: for the ADAS-cog14 score, -1.44 (95% CI, -2.27 to -0.61; $p < 0.001$); for the ADCOMS, -0.050 (95% CI, -0.074 to -0.027; $p < 0.001$); and for the ADCS-MCIADL score, 2.0 (95% CI, 1.2 to 2.8; $p < 0.001$).⁵⁶

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Aduhelm (aducanumab-awwa) and Leqembi (lecanemab-irmb) are A β -targeting antibody indicated for the treatment of Alzheimer's disease. Treatment with Aduhelm or Leqembi 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. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients receiving treatment. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

To monitor for Amyloid Related Imaging Abnormalities (ARIA), a recent (within one year) brain magnetic resonance imaging (MRI) prior to initiating treatment is required for Aduhelm or Leqembi. Aduhelm requires MRIs prior to the 5th, 7th, 9th and 12th infusion. 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. If 10 or more new incident microhemorrhages or > 2 focal areas of superficial siderosis (radiographic severe ARIA-H) is observed while receiving Aduhelm, treatment may be continued with caution only after a clinical evaluation and a follow-up MRI demonstrates radiographic stabilization (i.e., no increase in size or number of ARIA-H). Subsequent MRIs for Leqembi are recommended prior to the 5th, 7th, and 14th infusion.

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Policy History/Revision Information

Date	Summary of Changes
11/01/2023	<p>Notice of Revision: The following summary of changes has been modified. Revisions to the previous policy update announcement are outlined in red below. Please take note of the additional updates to be applied on Nov. 1, 2023.</p> <p>Application Texas</p> <ul style="list-style-type: none"> • Updated instruction to refer to the drug-specific criteria found within the <i>Texas Medicaid Provider Procedures Manual for Aduhelm and Leqembi</i> <p>Coverage Rationale Leqembi (lecanemab-irmb)</p> <ul style="list-style-type: none"> • Revised language to indicate: <ul style="list-style-type: none"> ○ Leqembi (lecanemab-irmb) may be covered for the treatment of Alzheimer’s disease (AD) in patients who meet all of the following criteria: <p>Initial Therapy</p> <ul style="list-style-type: none"> ▪ Diagnosis of one of the following based on National Institute on Aging and the Alzheimer’s Association (NIA-AA) criteria: <ul style="list-style-type: none"> – Mild cognitive impairment (MCI) due to Alzheimer’s disease – Probable Alzheimer’s disease dementia ▪ Submission of medical records (e.g., chart notes, laboratory values) documenting all of the following: <ul style="list-style-type: none"> – Global Clinical Dementia Rating (CDR) score of 0.5 or 1.0 – CDR Memory Box score of 0.5 or greater – One of the following: <ul style="list-style-type: none"> • Mini-Mental State Examination (MMSE) score of 22 or greater • Saint Louis University Mental Status (SLUMS) score of 17 or greater • Montreal Cognitive Assessment (MoCA) score of 17 or greater ▪ Submission of medical records (e.g., chart notes, laboratory values) documenting the presence of beta-amyloid protein deposition, as evidenced by one of the following: <ul style="list-style-type: none"> – Positive amyloid positron emission tomography (PET) scan – Both of the following: <ul style="list-style-type: none"> • Attestation that the patient does not have access to amyloid PET scanning • Cerebrospinal fluid (CSF) biomarker testing documents abnormalities suggestive of beta-amyloid accumulation in the brain (e.g., Aβ42: 40 ratio, p-tau/Aβ42); ▪ Other differential diagnoses [e.g., dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), vascular dementia, pseudodementia due to mood disorder, vitamin B12 deficiency, encephalopathy, etc.] have been ruled out ▪ One of the following: <ul style="list-style-type: none"> – Patient is not currently taking an anticoagulant (e.g., warfarin, dabigatran) – Both of the following: <ul style="list-style-type: none"> • Patient is currently taking an anticoagulant (e.g., warfarin, dabigatran) • Counseling has been provided that the combined use of Leqembi with anti-coagulant drugs may increase the risk of cerebral macrohemorrhage and prescriber attests that the patient has shared in decision-making to initiate Leqembi therapy ▪ Patient has no history of intracerebral hemorrhage [e.g., transient ischemic attack (TIA), stroke] within the previous year prior to initiating treatment

Date	Summary of Changes
	<ul style="list-style-type: none"> ▪ Counseling has been provided on the risk of amyloid-related imaging abnormalities (ARIA-E and ARIA-H) and patient is aware to monitor for headache, dizziness, visual disturbances, nausea, and vomiting ▪ Both of the following: <ul style="list-style-type: none"> – Counseling has been provided on how testing for ApoE ϵ 4 status informs the risk of developing ARIA when deciding to initiate treatment with Leqembi – Testing for ApoE ϵ 4 status has been offered to the patient and prescriber attests that the patient has shared in decision-making to initiate Leqembi therapy ▪ A baseline brain magnetic resonance imaging (MRI) has been completed within 12 months prior to initiating treatment ▪ Not used in combination with other Aβ monoclonal antibodies (mAbs) for Alzheimer's Disease (e.g., Aduhelm) ▪ Prescribed by a neurologist, geriatric psychiatrist, or geriatrician who specializes in treating dementia; and ▪ Prescriber attests that the prescriber's site is currently registered or will seek registration with the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) or other comparable patient registry that collects information on treatments for Alzheimer's disease, including Leqembi ▪ Leqembi dosing is in accordance with the U.S. FDA approved labeling ▪ Initial authorization will be for no more than 6 months <p>Continuation of Therapy</p> <ul style="list-style-type: none"> ▪ Patient continues to have one of following diagnoses based on National Institute on Aging and the Alzheimer's Association (NIA-AA) criteria: <ul style="list-style-type: none"> – Mild cognitive impairment (MCI) due to Alzheimer's disease – Probable Alzheimer's disease dementia; ▪ Submission of current medical records (e.g., chart notes, laboratory values) documenting that the patient continues to meet all of the following (updated assessments must be measured no earlier than 4 weeks prior to a continuation request): <ul style="list-style-type: none"> – Global Clinical Dementia Rating (CDR) score of 0.5 or 1.0 – CDR Memory Box score of 0.5 or greater – One of the following: <ul style="list-style-type: none"> • Mini-Mental State Examination (MMSE) score of 22 or greater • Saint Louis University Mental Status (SLUMS) score of 17 or greater • Montreal Cognitive Assessment (MoCA) score of 17 or greater ▪ Both of the following: <ul style="list-style-type: none"> – Submission of medical records (e.g., chart notes) confirming follow-up brain magnetic resonance imaging (MRI) has been completed after the initiation of therapy and prior to the 5th and 7th infusion treatment – One of the following: <ul style="list-style-type: none"> • ARIA has not been observed on MRI; or • ARIA has been observed on MRI, prescriber attests that continuation of therapy with Leqembi is appropriate based on the severity of the patient's clinical symptoms, and one of the following: <ul style="list-style-type: none"> ○ Follow-up MRI demonstrates radiographic resolution and/or stabilization ○ Prescriber attests that continuation of therapy with Leqembi is appropriate based on the radiographic severity of ARIA ▪ Not used in combination with other Aβ monoclonal antibodies (mAbs) for Alzheimer's Disease (e.g., Aduhelm) ▪ Prescribed by a neurologist, geriatric psychiatrist, or geriatrician who specializes in treating dementia ▪ Leqembi dosing is in accordance with the U.S. FDA approved labeling ▪ Reauthorization is for no more than 6 months

Date	Summary of Changes
	<ul style="list-style-type: none"> ○ Leqembi (lecanemab-irmb) is unproven and not medically necessary for any indication other than mild cognitive impairment due to Alzheimer’s disease and mild Alzheimer’s disease dementia <p>Applicable Codes</p> <ul style="list-style-type: none"> ● Added HCPCS code J0174 ● Removed HCPCS code J3590 <p>Supporting Information</p> <ul style="list-style-type: none"> ● Updated <i>Background</i>, <i>Clinical Evidence</i>, and <i>References</i> sections to reflect the most current information ● Archived previous policy version CS2023D0108C

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

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