Pharmacy Management Drug Policy

SUBJECT: Anti-Amyloid Directed Therapies
POLICY NUMBER: PHARMACY-100
EFFECTIVE DATE: 06/24/2021
LAST REVIEW DATE: 11/19/2025

If the member's subscriber contract excludes coverage for a specific service or prescription drug, it is not covered under that contract. In such cases, medical or drug policy criteria are not applied. This drug policy applies to the following line/s of business:

Policy Application

Category:	☒ Commercial Group (e.g., EPO, HMO, POS, PPO)	☒ Medicare Advantage
	☒ On Exchange Qualified Health Plans (QHP)	☐ Medicare Part D
	☒ Off Exchange Direct Pay	☒ Essential Plan (EP)
	☒ Medicaid & Health and Recovery Plans (MMC/HARP)	☒ Child Health Plus (CHP)
	☐ Federal Employee Program (FEP)	☐ Ancillary Services
	☒ Dual Eligible Special Needs Plan (D-SNP)	

DESCRIPTION:

Alzheimer's disease (AD) is a progressive brain disease characterized by decline in memory, thinking, and physical function. It is estimated that AD affects 6.2 million Americans 65 years of age and older and is the sixth leading cause of death in the United States.[1] Alzheimer's disease progresses on a continuum categorized by three phases: (1) preclinical AD (2) mild cognitive impairment (MCI) due to AD and (3) Alzheimer's dementia which is further classified into mild, moderate, and severe. As the disease progresses, noticeable symptom changes occur in memory, thinking, and behavioral, impacting the patient's ability to perform activities of daily living. Risk factors for late-onset AD include older age, mutations in the apolipoprotein e4 gene (APOE-e4), and family history of AD. Early-onset AD has been linked to several less common genetic mutations.[1] No single test is used to diagnose Alzheimer's dementia but rather a variety of assessments, cognitive tests, and biomarkers collectively assist in making the diagnosis.[2]

While the exact mechanism of the disease is not fully understood, several hypotheses exist that focus on different features of the disease including, but not limited to, accumulation of beta-amyloid proteins, abnormal formation of a protein called tau, inflammation, and cholinergic abnormalities.[3] Current and prospective drug targets aim at correcting these imbalances with recent focus on the accumulation of beta-amyloid plaques and neurofibrillary tangles of phosphorylated tau protein. It is believed that the accumulation of these plaques and tangles contribute to damage and death of neurons in the brain.[4,5]

Pharmacological treatments for Alzheimer's dementia include cholinesterase inhibitors (i.e., donepezil, rivastigmine, and galantamine) used primarily for early and intermediate AD and memantine, a glutamate antagonist, indicated for moderate to severe AD. These treatments have not been shown to stop or slow the disease progression but are used to treat cognitive and functional symptoms of the disease.[1]

The FDA announced on June 7th, 2021, the approval of Aduhelm (aducanumab-avwa), the first monoclonal antibody directed against amyloid-beta. On January 6th, 2023, the FDA approved the second anti-amyloid beta monoclonal antibody called Leqembi (lecanemab-irmb). On July 2nd, 2024, the FDA approved Kisunla.

All these drugs were studied in patients with Alzheimer's Disease with mild cognitive impairment or mild dementia and received accelerated approval based on reduction in amyloid beta plaques. There are no safety or effectiveness data on initiating these treatments at earlier or later stages of the disease than were studied. Phase III trials are underway for other anti-amyloid beta directed monoclonal antibodies, primarily in early stages of AD.

Additionally, other amyloid beta drug targets include beta-site amyloid precursor protein cleaving enzymes (BACEs), y-secretases, and inhibitors of beta-amyloid deposition (anti-aggregation compounds). While several clinical trials for these amyloid targeted therapies have demonstrated the intended mechanistic effects on beta-amyloid, this has yet to be translated into a clinical benefit. Limitations of these trials have been recognized, including the fact that many were studied in later stages of AD.[5]

ADUHELM (aducanumab-avwa)

Aduhelm (aducanumab-avwa) is an amyloid beta-directed antibody indicated for treatment of Alzheimer's disease. In July 2021, updates were made to the Aduhelm prescribing information to clarify treatment should be initiated in patients with MCI or mild dementia stage of disease, the same as the population studied in clinical trials. The label further states there is no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied.[6] The FDA approved Aduhelm (aducanumab-avwa) using the accelerated approval pathway, which allows for earlier approval of drugs to treat serious or life-threatening conditions based on a surrogate endpoint that is reasonably likely to predict a clinical benefit, but is not itself a measure of clinical benefit.[7,8] The surrogate endpoint used for this accelerated approval was reduction of amyloid beta plaque in the brain. Continued approval for this indication may be contingent upon verification of clinical benefit in a confirmatory trial.

The efficacy of Aduhelm (aducanumab-avwa) was evaluated in two double-blind, randomized, placebo-controlled parallel group Phase 3 studies (ENGAGE and EMERGE) and a Phase 1b trial (PRIME). Details from the ENGAGE and EMERGE trials are discussed below.[9,10]

On January 31, 2024, Biogen, the manufacturer of Aduhelm, announced plans to discontinue development and commercialization of Aduhelm and will terminate the Phase 4 ENVISION confirmatory study. The company noted that this decision was not related to safety or efficacy concerns. According to the manufacturer's website, updated on November 1, 2024, Aduhelm is no longer available.

ENGAGE and EMERGE TRIALS

Methods

For the Phase 3 trials (ENGAGE and EMERGE), patients 50-85 years of age were eligible to participate if they met criteria for MCI due to AD or mild AD dementia and had confirmed evidence of beta-amyloid by positron emission tomography (PET). Patients also had to meet the following criteria: Clinical Dementia Rating (CDR) global score of 0.5, Repeatable Battery for Assessment of Neuropsychological Status (RBANS) delayed memory index score $\leq$ 85, and Mini-Mental State Examination (MMSE) score of 24-30.

Patients in the ENGAGE trial and EMERGE trials were randomized in a 1:1:1 ratio to receive low-dose aducanumab (3 or 6 mg/kg given intravenously (IV) for APOE-e4 carriers and noncarriers, respectively), high-dose aducanumab (10 mg/kg given IV), or placebo every 4 weeks for 18 months. This was followed by an optional, dose-blind, long term extension period. An initial titration period of

up to 6 months occurred for both trials to the maximum target dose. Of note, initially APOE-e4 carriers were titrated to a maximum of 6 mg/kg in the high dose group, but this protocol was later adjusted to 10 mg/kg.

The primary endpoint was change from baseline in Clinical Dementia Rating-Sum of Boxes (CDR-SB) score at 18 months. The CDR-SB score assess cognition and function where a higher score indicates greater disease severity. Secondary endpoints assessed clinical decline measure by the Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale – Cognitive 13-Item Scale (ADAS-Cog 13), and Alzheimer's Disease Cooperative Study – Activities of Daily Living – Mild Cognitive Impairment (ADCS-ADL-MCI). Additionally, both trials included various biomarker sub-studies to assess brain amyloid by positron emission tomography (PET), beta-amyloid levels in the cerebrospinal fluid (CSF), intracellular tau accumulation in the CSF measured by phosphorylated tau (p-tau), neurodegeneration measured by CSF total Tau (t-Tau) and tau pathophysiology assessed by Tau PET.

Futility Analysis

An interim analysis for futility was prespecified in the study protocols to allow for early termination of the study if the drug was found to be ineffective in an effort to limit exposure to the placebo and drug. The results of the prespecified futility analysis showed futility and the ENGAGE and EMERGE trials were terminated prior to planned completion. After review of the futility analysis, it was determined that the two studies had differing results and to better understand this divergence the manufacturer conducted additional analysis with a larger dataset. The manufacturer in conjunction with the FDA determined that the use of this larger dataset was "interpretable and suitable for additional consideration".[9] The results using this larger dataset are outlined below.

Results

For the ENGAGE trial, neither treatment group had a statistically significant difference from placebo on the primary or secondary efficacy endpoints. Of the 1,647 patients in the ENGAGE study, 585 patients were enrolled in the amyloid PET subgroup with 347 evaluated at week 78. In the amyloid PET sub-study, compared to placebo, there was a statistically significant time and dose-dependent reduction in brain amyloid plaque measured by PET for both treatment groups. CSF levels of p-Tau and t-Tau were not significantly different from placebo.

Conversely, the EMERGE trial (N=1,638) showed a statistically significant improvement in the high-dose arm versus placebo in the primary outcome measure, CDR-SB (22% less decline, p=0.0120) and a numerical, though not statistically significant, improvement in the low-dose arm. Secondary endpoints related to MMSE, ADAS-Cog13 and ADCS-ADL-MCI were statistically improved compared to placebo in the high dose group. In the amyloid PET sub-study (N=488) a time and dose-dependent reduction in brain amyloid plaque was statistically significant in the treatment groups versus placebo. Similarly, CSF p-Tau and CSF t-Tau were statistically significantly reduced in the treatment group versus placebo (N=78).

The investigators concluded that the two trials were partially discordant. The low dose groups of both studies showed similar trends across clinical and biomarker measurements, but the high dose arms diverged on their respective endpoints. Investigators determined through a post-hoc exploratory analysis that two main factors may explain this difference. The first being patients in the ENGAGE study had lower exposure to the 10 mg/kg dosing which was an important factor for efficacy. Additionally, the investigators determined an imbalance in the number and distribution of rapid

progressing Alzheimer's disease patients in the high-dose group of the ENGAGE trial.[9] As previously noted, this was an exploratory post-hoc analysis which carries inherent limitations and therefore these results must be interpreted cautiously.

Aduhelm Safety

Combined safety data from the ENGAGE and EMERGE trial reported 90.7% of patients treated with aducanumab experienced an adverse effect compared to 86.9% in the placebo group. Adverse events with ≥5% incidence in the aducanumab 10 mg/kg group that exceeded the incidence in the placebo group by ≥2% includes: amyloid-related imaging abnormalities-edema (ARIA-E), headache, amyloid-related imaging abnormalities– hemorrhage or superficial siderosis (ARIA-H), fall, and diarrhea.

ARIA is associated with amyloid-modifying therapies and is seen on brain MRI. The MRI findings can include edema or effusion (ARIA-E) or brain microhemorrhage or localized superficial siderosis (ARIA-H).

FDA Advisory Committee Review

On November 6, 2020, the FDA Peripheral and Central Nervous System Drugs Advisory Committee convened to review the application for aducanumab for the treatment of Alzheimer's disease and vote on several questions posed to the Committee.[11]

When was asked if the EMERGE trial, independent of the ENGAGE trial, provides "strong evidence that supports the effectiveness of aducanumab for the treatment of Alzheimer's disease" the Committee voted: 1 yes, 8 no, and 2 uncertain. Additionally, the Committee was somewhat split on whether the manufacturer presented strong evidence of a pharmacodynamic effect on Alzheimer's disease pathophysiology with 5 members voting yes and 6 uncertain.

Almost all Committee members agreed (10 no, 1 uncertain) that it was not reasonable to consider the EMERGE study as primary evidence of effectiveness of aducanumab for the treatment of Alzheimer's disease. Members expressed reluctancy to suggest approval for aducanumab for the treatment of Alzheimer's disease because of insubstantial evidence. The individual who was uncertain did highlight that the EMERGE trial was positive, and the PRIME study provided some additional evidence.

The Institute for Clinical and Economic Review (ICER)

ICER is a non-profit research organization that evaluates clinical and economic evidence for the value of prescription drugs, medical tests, devices, and health system innovations. ICER compiled an evidence report of aducanumab from both a clinical and economic perspective.[12] In a statement released on June 7, 2021, following the FDA-approval of Aduhelm (aducanumab), ICER stated:

"Our review of the evidence was concordant with that of many independent experts: **current evidence is insufficient to demonstrate that aducanumab benefits patients**. The avenue forward has seemed clear: another study would be needed to reduce the substantial uncertainty about the drug's effectiveness, a requirement of even greater priority because of the drug's common and potentially serious side effects."[13]

LEQEMBI (lecanemab-irmb)

Leqembi (lecanemab-irmb) is the second amyloid beta-directed antibody indicated for the treatment of Alzheimer's disease and should only be initiated in patients with mild cognitive impairment or mild dementia stage of disease. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied.
The efficacy of Leqembi (lecanemab-irmb) was evaluated in one Phase IIb study (Study 1) and one Phase III study (CLARITY AD).[14,15] Results from Study 1 demonstrated a reduction in amyloid beta plaque which served as the basis for FDA approval under the accelerated approval pathway.

On January 6th, 2023, it was announced that data from the confirmatory CLARITY AD trial was submitted to the FDA as part of a supplemental Biologics License Application (sBLA) to convert the accelerated approval to a traditional approval. On July 6th, 2023, the FDA converted Leqembi to traditional approval based on the confirmatory trial CLARITY AD.

Study 1

Methods

Patients 50 to 90 years of age were eligible to participate if they met criteria for MCI due to AD or mild AD dementia and had confirmed evidence of beta-amyloid by PET scan or cerebrospinal fluid (CSF) beta-amyloid$_{1-42}$. Additionally, patients had to have objective impairment in episodic memory on Wechsler Memory Scale-IV Logical Memory II, Mini Mental State Examination (MMSE) score greater than or equal to 22. Patients were also required to have a Clinical Dementia Rating Scale global score of 0.5 or 1.0 with a Memory Box score of ≥ 0.5. Patients were excluded from the study for any neurologic condition (other than Alzheimer's disease), history of transient ischemic attacks, stroke, or seizures, or significant pathological findings on brain MRI.

The study included a 2-month screening period, an 18-month (78-week) placebo-controlled treatment period, and a safety follow-up period of 3 months after the final dose. During the placebo-controlled treatment period, patients were randomized to placebo or one of five lecanemab dosing regimen: 3 arms with biweekly (once every 2 weeks) dosing (2.5, 5, and 10 mg/kg) and 2 arms with monthly (once every 4 weeks) dosing (5 and 10 mg/kg). Of note, during the study, the protocol was amended so that ApoE ε4 carriers were no longer randomized to the 10 mg/kg every two weeks dose arm. ApoE ε4 carriers who had been receiving Leqembi 10 mg/kg every two weeks for 6 months or less were discontinued from the study drug. This was based on data indicating that ApoE ε4 homozygotes on the highest dose of Leqembi (10mg/kg once every 2 weeks) had the highest risk of developing symptomatic ARIA-E.

The primary endpoint was change from baseline at 12 months on Alzheimer's Disease Composite Score (ADCOMS). Secondary endpoints included change from baseline at 18 months in brain amyloid by PET Standard Uptake Value ratio (SUVr), score on the ADCOMS, CDR-SB, and ADAS-Cog14.

Results

Leqembi dosed 10 mg/kg once every 2 weeks was identified as the target dose. Leqembi reached a 64% probability of being better than placebo with 25% less decline at 12 months in the ADCOMS, missing the pre-specified 80% probability threshold. Therefore, the primary endpoint was not met.

A total of 315 patients were enrolled in the amyloid PET sub-study and of those 277 had results evaluated at week 79. Lecanemb 10 mg/kg once every 2 weeks had a statistically significant

decrease in brain amyloid plaque as measured by PET quantified by a composite SUVr when compared to placebo at Week 79 (-0.310, p<0.001). The FDA concluded, based on the surrogate endpoint of reduction in amyloid plaque burden, there was data to support the accelerated approval of Leqembi.

CLARITY AD

Methods

Eligible patients were 50 to 90 years with MCI or mild AD dementia with confirmed evidence of beta-amyloid by PET scan or cerebrospinal fluid (CSF). Inclusion and exclusion criteria were similar to Study 1.
The trial design included a screening period, followed by an 18-month (78-week) placebo-controlled treatment period, and a safety follow-up period of 3 months. Patient were randomized in a 1:1 fashion to either Leqembi 10 mg/kg IV once every 2 weeks or placebo for 18 months.

The primary efficacy endpoint was change from baseline at Week 78 on the CDR-SB scale, where higher scores indicate greater impairment. Secondary endpoints included change from baseline at 18 months in amyloid on PET scan, score on the ADAS-Cog14, ADCOMS, and Alzheimer's Disease Cooperative Study-Activities of Daily Living-Mild Cognitive Impairment (ADCS-ADL-MCI).

Results

Of the 1,795 participates, 898 received Leqembi and 897 received placebo. Baseline characteristics were similar between the two groups. Of note, 31% of participants were ApoE ε4 noncarriers. At 18 months, the adjusted mean change from baseline in CDR-SB score was 1.21 in the Leqembi arm and 1.66 in the placebo arm (treatment difference of -0.45; 95% confidence interval [CI]: -0.67 to -0.23; P < 0.001). The sub-study of amyloid burden on PET included 698 participants and found the adjusted mean change from baseline at 18 months was -55.48 centiloids in the Leqembi arm and 3.64 centiloids in the placebo arm (treatment difference -59.12 centiloids; 95% CI: -62.64, -55.60; P < 0.001).

Leqembi Safety

Leqembi carriers a warning regarding ARIA. In Study 1, symptomatic ARIA occurred in 3% of patients treated with Leqembi. Clinical symptoms resolved in 80% of patients during the observation period. When including asymptomatic radiographic events, 12% of Leqembi treated patients versus 5% of patients on placebo had observed ARIA. ARIA-E was seen in 10% of Leqembi treated patients versus 1% in the placebo group. ARIA-H was seen in 6% and 5% of patients treated with Leqembi and placebo, respectively.

ARIA was higher in Leqembi treated patients who were ApoE ε4 homozygotes when compared to heterozygotes and noncarriers. Leqembi prescribing information gives consideration for testing ApoE ε4 status to gauge risk of developing ARIA before starting Leqembi treatment. Additionally, the prescribing information outlines monitoring and dosing interruption protocols for ARIA.

Leqembi can cause infusion-related reactions and may require infusion rate reductions or premedication at subsequent dosing.

The most common adverse reactions in patients treated with Leqembi (incidence approximately 10% and a higher rate compared to placebo): infusion-related reactions (20%), headache (14%), and ARIA-edema (10%).

Kisunla (donanemab-azbt)

Kisunla (donanemab-azbt) is the third amyloid beta-directed antibody indicated for the treatment of Alzheimer's disease and should only be initiated in patients with mild cognitive impairment or mild dementia stage of disease.

The efficacy of Kisunla was evaluated in one Phase III pivotal study (TRAILBLAZER-ALZ2) in patients with early symptomatic Alzheimer disease (mild cognitive impairment or Alzheimer disease with mild dementia) and a Phase II supportive study (TRAILBLAZER-ALZ). The FDA approved Kisunla based on safety and efficacy evidence from TRAILBLAZER-ALZ2. The benefit of Kisunla was evaluated based on several clinical scales including the integrated Alzheimer's Disease Rating Scale (iADRS) and the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB).

TRAILBLAZER-ALZ2

Methods

Patients 60 to 85 years of age were eligible to participate if they met criteria for MCI or mild AD dementia and had confirmed amyloid and low/medium or high tau pathology based on PET imaging. Additionally, patients had to have gradual and progressive change in memory function reported by participants or informants for ≥ 6 months and Mini Mental State Examination (MMSE) score of 20 to 28 at baseline. Patients were excluded from the study if they had a contraindication to MRI or PET scans or current treatment with immunoglobulin G (IgG) therapy.[18]

TRAILBLAZER-ALZ 2 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, 18-month trial that enrolled 1736 participants with early symptomatic Alzheimer disease (mild cognitive impairment/mild dementia) with amyloid and low/medium or high tau pathology based on PET imaging. Participants were randomized in a 1:1 ratio to receive donanemab (n = 860) or placebo (n = 876) intravenously every 4 weeks for 72 weeks. Participants in the donanemab group were switched to receive placebo in a blinded manner if the amyloid plaque level was <11 Centiloids on a single PET scan or 11 to <25 Centiloids on 2 consecutive PET scans measured at Week 24, Week 52, and Week 76.[18]

The primary endpoint was the change in integrated Alzheimer Disease Rating Scale (iADRS) score from baseline to 76 weeks (range, 0-144; lower scores indicate greater impairment). There were 24 gated outcomes (primary, secondary, and exploratory), including the secondary outcome of change in the sum of boxes of the Clinical Dementia Rating Scale (CDR-SB) score (range, 0-18; higher scores indicate greater impairment).

Results

The LSM change from baseline at Week 76 in the iADRS score was -6.02 in the Kisunla arm and -9.27 in the placebo arm (treatment difference 3.25; $P < 0.001$), representing a 35.1% slowing of disease progression in the low/medium tau population. In the combined population, the LSM change from baseline at Week 76 in the iADRS score was -10.19 in the Kisunla arm and -13.11 in the placebo arm (treatment difference 2.92; $P < 0.001$), representing a 22.3% slowing of disease progression. [18]

In the low/medium tau population, the placebo-adjusted LSM change from baseline at 76 weeks for CDR-SB was -0.67 (36.0% slowing of clinical progression), and in the combined population, the placebo-adjusted LSM change from baseline at 76 weeks for CDR-SB was -0.70 (28.9% slowing of clinical progression).

TRAILBLAZER-ALZ

Methods

Patients 60 to 85 years of age were eligible to participate if they met criteria for MCI or mild AD dementia and had confirmed amyloid and tau pathology based on PET imaging. Additionally, patients had to have gradual and progressive change in memory function reported by participants or informants for ≥ 6 months and Mini Mental State Examination (MMSE) score of 20 to 28 at baseline or an acceptable historical flortaucipir PET scan within 6 months prior to baseline that meets the central read criteria. Patients were excluded from the study if they had a history of long QT syndrome, received treatment with a stable dose of an acetylcholinesterase inhibitor (AChEI) and/or memantine for less than 2 months before randomization, or contraindication to MRI.[19]

TRAILBLAZER-ALZ is a Phase 2, multicenter, randomized, double-blind, placebo-controlled trial of donanemab in 257 patients with early symptomatic Alzheimer's disease who had tau and amyloid deposition on PET imaging. Patients were randomly assigned in a 1:1 ratio to receive donanemab (n=131) or placebo (n=126) intravenously every 4 weeks for up to 72 weeks.

The primary endpoint was the change from baseline in the score on the Integrated Alzheimer's Disease Rating Scale (iADRS; range, 0 to 144, with lower scores indicating greater cognitive and functional impairment) at 76 weeks. Secondary outcomes included the change in scores on the Clinical Dementia Rating Scale–Sum of Boxes (CDR-SB), the 13-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog_{13}), the Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living Inventory (ADCS-iADL), and the Mini–Mental State Examination (MMSE), as well as the change in the amyloid and tau burden on PET.

Results

The change from baseline in the iADRS score at 76 weeks was -6.86 in the Kisunla arm and -10.06 in the placebo arm (treatment difference 3.20; P = 0.04). The placebo-adjusted change from baseline at 76 weeks for the CDR-SB score was -0.36 (95% CI: -0.83, 0.12) and failed to show a significant difference between the two trial groups.[19]

Kisunla Safety

Kisunla carriers a warning regarding ARIA. In TRAILBLAZER-ALZ2, Symptomatic ARIA occurred in 6% (52/853) of patients treated with KISUNLA. Clinical symptoms associated with ARIA resolved in approximately 85% (44/52) of patients. For 1.6% of participants in the donanemab treatment group, amyloid-related imaging abnormalities led to serious outcomes, such as hospitalization, and required supportive care and/or corticosteroid use. Three deaths in TRAILBLAZER-ALZ 2 occurred after serious amyloid-related imaging abnormalities.

Additional information in patients who are homozygous for apolipoprotein E (ApoE)-e4 and those taking antithrombotic therapy is warranted. safety monitoring is recommended with Kisunla including MRI assessments prior to initiation, as well as at certain timepoints after commencement of therapy, and requires enhanced vigilance. Kisunla is associated with very serious risks (various types of ARIAs) which are also associated with use of Leqembi.

The most common AEs in patients treated with Kisunla (vs. placebo) were ARIA-E (24% vs. 2%), ARIA-H microhemorrhage (25% vs. 11%), ARIA-H superficial siderosis (15% vs. 3%), headache (13% vs. 10%), and infusion-related reactions (9% vs. 0.5%). The rate of drug discontinuation due to AEs was 13% for Kisunla vs. 4% for placebo. The most common AE leading to discontinuation of Kisunla was infusion-related reactions (4% vs. 0). These AEs are similar to other medications in this class; however, the rate of ARIA may be somewhat increased vs. placebo for Kisunla.

RATIONALE:

Aduhelm (aducanumab-avwa)
Based on the inconsistencies in ENGAGE and EMERGE clinical trial data for Aduhelm (aducanumab-avwa), there is insufficient data to establish clinically meaningful effectiveness that leads to improved health outcomes for treatment of Alzheimer's disease. Additionally, when taking into consideration the higher incidence of ARIA compared to placebo, there is insufficient evidence to suggest that the clinical benefit of Aduhelm (aducanumab-avwa) outweighs the potential risks of therapy.

Leqembi (lecanemab-irmb)
In Study 1, Leqembi (lecanemab-irmb) demonstrated statistically significant reduction in amyloid plaque burden but did not achieve the primary efficacy endpoint. Although CLARITY AD demonstrated a statistically significant reduction of worsening in the CDR-SB score compared to placebo, the absolute difference of 0.45 is less than the minimal clinically important difference (MCID) of 1-2 points cited in the literature.[16,17]

Based on the currently available literature for Leqembi (lecanemab-irmb), there is insufficient data to establish clinically meaningful effectiveness that leads to improved health outcomes for the treatment of Alzheimer's disease. Additionally, when taking into consideration the higher incidence of ARIA compared to placebo, there is insufficient evidence to suggest that the clinical benefit of Leqembi (lecanemab-irmb) outweighs the potential risks of therapy.

Kisunla (donanemab-azbt)

In the Phase III, pivotal TRAILBLAZER-ALZ2 study, the primary efficacy endpoint for Kisunla™ (donanemab-azbt) was change from baseline in the integrated Alzheimer's Disease Rating Scale (iADRS) at 76 weeks. The low/medium tau population demonstrated a least-square mean (LSM) change from baseline at Week 76 in the iADRS of -6.02 compared to -9.27 in the placebo group, representing a 3.25-point treatment difference (P<0.001). In the combined low/medium and high tau population, the LSM change from baseline at week 76 in iADRS score for Kisunla was -10.19 compared to -13.11 in the placebo group (treatment difference of 2.92, P<0.001). The key secondary endpoint of change from baseline at Week 76 in Clinical Dementia Rating Scale-sum of boxes (CDR-SB) demonstrated a placebo-adjusted LSM change of -0.67 in the low/medium tau group and -0.70 in the combined population. Although these results demonstrate statistical significance, clinical significance was not met. As cited in the literature, the minimal clinically important difference is 5 points for MCI due to AD and 9 points for AD with mild dementia and 1-2 points for CDR-SB.[17,18] Additionally, the Phase II TRAILBLAZER-ALZ study demonstrated a statistically significant change in

iADRS score of -6.86 for the Kisunla arm and -10.06 in the placebo arm (treatment difference of 3.20;P=0.04), but did not achieve statistical significance versus placebo in CDR-SB.[19]

Therefore, there is insufficient data to establish clinically meaningful effectiveness that leads to improved health outcomes for the treatment of Alzheimer's disease. Additionally, when taking into consideration the higher incidence of ARIA compared to placebo, there is insufficient evidence to suggest that the clinical benefit outweighs the potential risks of this therapy.

POLICY:

Aduhelm (aducanumab-avwa):

On January 31, 2024, the manufacturer of Aduhelm announced that it would discontinue development and commercialization of Aduhelm (aducanumab-avwa) and will terminate the ENVISION clinical study. This decision was not related to safety or efficacy concerns. According to the manufacturer's website, updated on November 1, 2024, Aduhelm is no longer available.

Based on the above announcement, The Health Plan will not authorize coverage for Aduhelm for new patients or existing users.

Legembi (lecanemab-irmb) (Medical) and Legembi Iqlik (lecanemab-irmb) (Rx) coverage varies by line of business as below:

Commercial/Exchange/Essential/criteria:

1. Based upon our criteria and assessment of the peer-reviewed evidence, the use of Leqembi (lecanemab-irmb) has not been medically proven to be effective and, therefore, is considered **investigational** for the treatment of Alzheimer's disease. The justification for Leqembi (lecanemab-irmb) to be considered investigational is as follows:
    a. Based upon our assessment of the peer-reviewed medical literature, there is inconclusive evidence that the drug has a definite positive effect on health outcomes.
    b. Based upon our assessment of the peer-reviewed medical literature, there is inconclusive evidence that the drug, over time, leads to improvement in health outcomes (e.g., the beneficial effects of the service outweigh any harmful effects).
    c. Based upon our assessment of peer-reviewed medical literature, there is inconclusive evidence that the drug provides improvement in health outcomes in standard conditions of medical practice, outside the clinical investigatory settings.

Refer to Corporate Medical Policy #11.01.03 Experimental or Investigational Services

Medicare Advantage and D-SNP Plans:

Medicare reviews are to follow the national coverage determination (NCD) issued by CMS effective 12/12/2022. The NCD can be found on the CMS website at: https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=375&ncdver=1

Medicaid Managed Care (MMC)/Health and Recovery Plans (HARP) and Child Health Plus:

1. Must be 50 years of age or older **AND**
2. Must be prescribed by a geriatrician, neurologist, geriatric psychiatrist, or Dementia and Alzheimer's disease specialist **AND**

3. Must have a diagnosis of Mild Cognitive Impairment (MCI) due to Alzheimer's disease (AD) or have mild AD **AND**
    a. Documentation of a mini mental state examination (MMSE) score of 22-30 **AND**
    b. Documentation of <u>one</u> additional validated cognitive assessment tool indicating MCI due to Alzheimer's disease or mild Alzheimer's disease (e.g., Montreal Cognitive Assessment Test (MoCA), Alzheimer Disease Assessment Scale-Cognitive subscale 14 (ADAS-Cog 14), the Saint Louis University Mental Status Examination (SLUMS), Self-Administered Gerocognitive Exam (SAGE), Clinical Dementia Rating (CDR) Global score) **AND**
4. Must have positive biomarker for brain amyloid pathology documented by:
    a. Positron Emission Tomography (PET) scan **OR**
    b. Cerebrospinal fluid (CSF)**AND**
5. Prescriber must attest that <u>ONE</u> of the following must has been met:
    a. Patient has documentation of genetic testing to determine apolipoprotein E4 ε4 (ApoE ε4) status and the prescriber has informed patient of the risk of developing Amyloid Related Imaging Abnormalities (ARIA) based on genotype results **OR**
    b. Genetic testing has not been performed, and the prescriber has informed the patient that it cannot be determined if they are ApoE ε4 homozygotes and at higher risk for ARIA **AND**
6. Must have documentation of a recent (within one year) brain magnetic resonance imaging (MRI) prior to initiating treatment **AND**
7. Prescriber must attest that an MRI will be performed prior to the 3rd, 5th, 7th, and 14th infusions in accordance with FDA labeling **AND**
8. Prescriber must attest that the patient must not have any medical condition, neurological condition (other than Alzheimer's Disease), or laboratory abnormalities that may be a contributing cause of the patient's cognitive impairment. (Examples include but are not limited to: Lewy Body Dementia, Frontotemporal Dementia, Parkinson's Disease dementia, Alcoholic Dementia, Vascular Dementia, Drug-Induced Amnestic Syndrome, Posterior Cortical Atrophy, Progressive Supranuclear Palsy, Traumatic Brain Injury, Mixed Dementia, Uncontrolled Hypothyroidism, Vitamin B12 Deficiency, Electrolyte and/or CBC abnormalities known to impair cognition.) **AND**
9. Coverage of Leqembi will be excluded if <u>any</u> of the following are true:
    a. Patient had a transient ischemic attack (TIA), stroke, or seizures within the previous 12 months.
    b. Patient is unable to obtain MRI scanning (i.e. cardiac pacemaker/defibrillator, ferromagnetic metal implants not approved as safe for use in MRI scanners).
    c. Patient has evidence of other clinically significant lesions that could indicate dementia diagnosis other than AD on brain MRI or other significant pathological findings on brain MRI <u>including **any** of the following</u>:
        i. More than 4 microhemorrhages (defined as 10 mm or less at the greatest diameter)
        ii. A single macrohemorrhage greater than 10 mm at greatest diameter
        iii. An area of superficial siderosis
        iv. Evidence of vasogenic edema
        v. Evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions
        vi. Evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease
        vii. Space occupying lesions
        viii. Brain tumors (note: lesions diagnosed as meningiomas or arachnoid cysts and <1cm at their greatest diameter may be permitted for treatment with Leqembi)
10. For patients on concomitant antithrombic medications (aspirin, other antiplatelets, or anticoagulants), must be on a stable dose for at least 4 weeks prior to initiating Leqembi **AND**

11. Initial approval and recertification requests will be for 12 months at a time and will require the following:
    a. Patient is tolerating therapy and has not experienced Amyloid Related Imaging Abnormalities - Edema (ARIA-E) or Amyloid Related Imaging Abnormalities -Hemosiderin Deposition (ARIA-H) events **OR**
    b. Patient has had ARIA-E and/or ARIA-H event(s) and documentation is provided that the appropriate dosing recommendations and monitoring have been followed as per the FDA-labeling to warrant continued treatment with Leqembi **AND**
    c. Documentation of a follow-up MRI prior to 3rd, 5th, 7th, and 14th infusions are provided (*Only applicable for the first recertification request*) **AND**
    d. Documentation of:
        i. MMSE score of 22-30 **AND**
        ii. Stable (i.e. not progressed to moderate or severe AD) or improved cognitive assessment score from baseline, demonstrated by at least one of the validated cognitive assessment tools used for the initial request in criterion #3b. **AND**
    e. Prescriber attests the patient's disease has not progressed to moderate or severe AD
12. The recommended starting dosage of Leqembi is 10 mg/kg as an intravenous infusion over approximately one hour, once every two weeks for 18 months. After 18 months, continue treatment once every 2 weeks or transition to an intravenous or subcutaneous maintenance dosage.
        i. Recommended maintenance dosage:
            1. Intravenous infusion: 10 mg/kg once every 4 weeks or
            2. Subcutaneous injection: 360 mg administered once a week using the Leqembi Iqlik autoinjector
13. Quantity Limit (Pharmacy Benefit)
    - Leqembi Iqlik: 4 prefilled autoinjectors per 28 days

Kisunla (donanemab-azbt) coverage varies by line of business as below:

Commercial/Exchange/Essential/criteria:

1. Based upon our criteria and assessment of the peer-reviewed evidence, the use of Kisunla (donanemab-azbt) has not been medically proven to be effective and, therefore, is considered investigational for the treatment of Alzheimer's disease. The justification for Kisunla (donanemab-azbt) to be considered investigational is as follows:
    a. Based upon our assessment of the peer-reviewed medical literature, there is inconclusive evidence that the drug has a definite positive effect on health outcomes.
    b. Based upon our assessment of the peer-reviewed medical literature, there is inconclusive evidence that the drug, over time, leads to improvement in health outcomes (e.g., the beneficial effects of the service outweigh any harmful effects).
    c. Based upon our assessment of peer-reviewed medical literature, there is inconclusive evidence that the drug provides improvement in health outcomes in standard conditions of medical practice, outside the clinical investigatory settings.

Refer to Corporate Medical Policy #11.01.03 Experimental or Investigational Services

For Medicare Advantage and D-SNP Plans:

1. Medicare reviews are to follow the national coverage determination (NCD) issued by CMS. The NCD can be found on the CMS website at: NCD - Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (AD) (200.3) (cms.gov)

For Medicaid Managed Care (MMC)/ Health and Recovery Plans (HARP) and Child Health Plus:

1. Must be 60 years of age or older **AND**
2. Must be prescribed by a geriatrician, neurologist, geriatric psychiatrist, or Dementia and Alzheimer's disease specialist **AND**
3. Must have a diagnosis of Mild Cognitive Impairment (MCI) due to Alzheimer's disease (AD) or have mild AD **AND**
    a. Documentation of a mini mental state examination (MMSE) score of 20-28 **AND**
    b. Documentation of one additional validated cognitive assessment tool indicating MCI due to Alzheimer's disease or mild Alzheimer's disease (e.g., Montreal Cognitive Assessment Test (MoCA), Alzheimer Disease Assessment Scale-Cognitive subscale 14 (ADAS-Cog 14), the Saint Louis University Mental Status Examination (SLUMS), Self-Administered Gerocognitive Exam (SAGE), Clinical Dementia Rating (CDR) Global score) **AND**
4. Must have positive biomarker for brain amyloid pathology documented by:
    a. Positron Emission Tomography (PET) scan **OR**
    b. Cerebrospinal fluid (CSF) **AND**
5. Prescriber must attest that ONE of the following must has been met:
    a. Patient has documentation of genetic testing to determine apolipoprotein E4 ε4 (ApoE ε4) status and the prescriber has informed patient of the risk of developing Amyloid Related Imaging Abnormalities (ARIA) based on genotype results **OR**
    b. Genetic testing has not been performed and the prescriber has informed the patient that it cannot be determined if they are ApoE ε4 homozygotes and at higher risk for ARIA **AND**
6. Must have documentation of a recent (within one year) brain magnetic resonance imaging (MRI) prior to initiating treatment **AND**
7. Prescriber must attest that an MRI will be performed prior to the 2nd, 3rd, 4th, and 7th infusions in accordance with FDA labeling **AND**
8. Prescriber must attest that the patient must not have any medical condition, neurological condition (other than Alzheimer's Disease), or laboratory abnormalities that may be a contributing cause of the patient's cognitive impairment. (Examples include but are not limited to: Lewy Body Dementia, Frontotemporal Dementia, Parkinson's Disease dementia, Alcoholic Dementia, Vascular Dementia, Drug-Induced Amnestic Syndrome, Posterior Cortical Atrophy, Progressive Supranuclear Palsy, Traumatic Brain Injury, Mixed Dementia, Uncontrolled Hypothyroidism, Vitamin B12 Deficiency, Electrolyte and/or CBC abnormalities known to impair cognition.) **AND**
9. Coverage of Kisunla will be excluded if any of the following are true:
    a. Patient had a transient ischemic attack (TIA), stroke, or seizures within the previous 12 months.
    b. Patient is unable to obtain MRI scanning (i.e. cardiac pacemaker/defibrillator, ferromagnetic metal implants not approved as safe for use in MRI scanners).
    c. Patient has evidence of other clinically significant lesions that could indicate dementia diagnosis other than AD on brain MRI or other significant pathological findings on brain MRI including **any** of the following:
        i. Presence of ARIA-E
        ii. More than 4 microhemorrhages
        iii. Any macrohemorrhage or severe white matter disease
        iv. More than 1 area of superficial siderosis
10. For patients on concomitant antithrombic medications (aspirin, other antiplatelets, or anticoagulants), must be on a stable dose for at least 4 weeks prior to initiating Kisunla
11. Initial approval and recertification requests will be for 12 months at a time and will require the following:

a. Patient is tolerating therapy and has not experienced Amyloid Related Imaging Abnormalities -Edema (ARIA-E) or Amyloid Related Imaging Abnormalities -Hemosiderin Deposition (ARIA-H) events **OR**
b. Patient has had ARIA-E and/or ARIA-H event(s) and documentation is provided that the appropriate dosing recommendations and monitoring have been followed as per the FDA-labeling to warrant continued treatment with Kisunla **AND**
c. Documentation of a follow-up MRI prior to 2nd, 3rd, 4th, and 7th infusions are provided (*Only applicable for the first recertification request*) **AND**
d. Documentation of:
    i. MMSE score of 20-28 **AND**
    ii. Stable (i.e. not progressed to moderate or severe AD) or improved cognitive assessment score from baseline, demonstrated by at least one of the validated cognitive assessment tools used for the initial request in criterion #3b. **AND**
e. Prescriber attests the patient's disease has not progressed to moderate or severe AD
f. Administer Kisunla as an intravenous infusion over approximately 30 minutes every four weeks as follows
    i. Infusion 1: 350 mg
    ii. Infusion 2: 700 mg
    iii. Infusion 3: 1,050 mg
    iv. Infusion 4 and beyond: 1,400 mg

POLICY GUIDELINES:

1. Prior authorization is contract dependent
2. Not all contracts cover all Medical Infusible drugs. Refer to specific contract/benefit plan language for exclusions of Injectable Medications.
3. Leqembi intravenous infusion, and Kisunla are administered by a healthcare professional and will be considered for coverage under the medical benefit. Leqembi Iqlik is self-administered and will be considered for coverage under the pharmacy benefit.
5. Unless otherwise stated above within the criteria, approval time-period will be for 1 year.
    - Continued approval at time of recertification will require documentation that the drug is providing ongoing benefit to the patient in terms of improvement or stability in disease state or condition.
6. Clinical documentation must be submitted for each request (initial and recertification) unless otherwise specified (e.g., provider attestation required). Supporting documentation includes, but is not limited to, progress notes documenting previous treatments/treatment history, diagnostic testing, laboratory test results, genetic testing/biomarker results, imaging and other objective or subjective measures of benefit which support continued use of the requested product is medically necessary. Also, ongoing use of the requested product must continue to reflect the current policy's preferred formulary. Recertification reviews may result in the requirement to try more cost-effective treatment alternatives as they become available (i.e., generics, biosimilars, or other guideline supported treatment options). Requested dosing must continue to be consistent with FDA-approved or off-label/guideline-supported dosing recommendations.
7. This policy does not apply to Medicare Part D and D-SNP pharmacy benefits. The drugs in this policy may apply to all other lines of business including Medicare Advantage.
8. For members with Medicare Advantage, medications with a National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) will be covered pursuant to the criteria outlined by the NCD and/or LCD. NCDs/LCDs for applicable medications can be found on the CMS website at https://www.cms.gov/medicare-coverage-database/search.aspx. Indications that have not been addressed by the applicable medication's LCD/NCD will be covered in accordance

with criteria determined by the Health Plan (which may include review per the Health Plan's Off-Label Use of FDA Approved Drugs policy). Step therapy requirements may be imposed in addition to LCD/NCD requirements.

9. All requests will be reviewed to ensure they are being used for an appropriate indication and may be subject to an off-label review in accordance with our Off-Label Use of FDA Approved Drugs Policy (Pharmacy-32).
10. All utilization management requirements outlined in this policy are compliant with applicable New York State insurance laws and regulations. Policies will be reviewed and updated as necessary to ensure ongoing compliance with all state and federally mandated coverage requirements.
11. Manufacturers may either discontinue participation in, or may not participate in, the Medicaid Drug Rebate Program (MDRP). Under New York State Medicaid requirements, physician-administered drugs must be produced by manufacturers that participate in the MDRP. Products made by manufacturers that do not participate in the MDRP will not be covered under Medicaid Managed Care/HARP lines of business. Drug coverage will not be available for any product from a non-participating manufacturer. For a complete list of New/Reinstated & Terminated Labelers please visit: https://www.medicaid.gov/medicaid/prescriptiondrugs/medicaid-drug-rebate-program/newreinstated-terminated-labeler-information/index.html

CODES:

Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract. Codes may not be covered under all circumstances. Please read the policy and guidelines statements carefully.
Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.
Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).

HCPCS:

Drug Name	J-Code (if assigned)	NDC
Aduhelm	J0172	64406-101-01 64406-102-02
Leqembi	J0174	62856-0212-01 62856-0215-01
Kisunla	J0175	0002-9401-01

UPDATES:

Date	Revision
11/19/2025	Revised
10/03/2025	Revised
08/14/2025	Reviewed / P&T Committee Approval 08/14/2025
07/25/2025	Revised
03/06/2025	Revised
02/10/2025	Revised
12/16/2024	Revised
09/13/2024	Revised
08/16/2024	Revised
08/15/2024	Reviewed / P&T Committee Approval 08/15/2024

06/20/2024	Revised
09/23	Revised / P&T Committee Approval 08/24/2023
07/23	Revised
02/23	Revised / P&T Committee Approval 02/09/2023
12/22	Revised
08/22	Revised
07/22	P&T Committee Approval
2/22	Revised
1/22	Revised
9/21	Revised
7/21	P&T Committee Approval
7/21	Revised
6/21	Created

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