Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCPSY006.1224	**PSYCOTHERAPEUTIC AND NEUROLOGICAL AGENTS** **ANTI-AMYLOID MONOCLONAL ANTIBODIES** See Table 1 for Medications
Effective Date: 2/1/2025	**Review/Revised Date**: 08/24, 12/24 (snm)
Original Effective Date: 04/24	**P&T Committee Meeting Date**: 02/24, 10/24, 12/24
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

REQUIRED MEDICAL INFORMATION:
Medicare Part B:
Requests for Aduhelm (aducanumab-avwa) and Leqembi (lecanemab-irmb), for the treatment of Alzheimer's disease, may be covered when the following criteria are met:

1. **Initial authorization:**
    a. Documentation confirming diagnosis of mild cognitive impairment or early dementia caused by Alzheimer's disease
    b. Documentation confirming the presence of amyloid beta pathology prior to initiating treatment
    c. Medication is prescribed by a qualified physician with an appropriate clinical team and follow up care
    d. Member and/or prescriber is enrolled in an eligible registry/clinical trial in accordance with the Centers for Medicare & Medicaid Services (CMS) National Coverage Determination (Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (200.3))

2. **Reauthorization:**

a. Member has obtained an MRI prior to subsequent infusions as outlined in the applicable package label. If radiographically observed ARIA occurs, treatment is adjusted based on type, severity, and presence of symptoms
b. Continued enrollment in an eligible registry/clinical trial in accordance with the Centers for Medicare & Medicaid Services (CMS) National Coverage Determination (Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (200.3))

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a neurologist or provider that specializes in the treatment of Alzheimer's disease

COVERAGE DURATION:
Initial and reauthorization will be approved for six months

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Aducanumab (Aduhelm®), donanemab (Kisunla®) and lecanemab (Leqembi®) are monoclonal antibodies that target the buildup of amyloid plaque in the brain.

FDA APPROVED INDICATIONS:

Table 1. Drugs applicable to this policy

Drug	FDA Indication

Aducanumab-avwa (Aduhelm®)	For the treatment of Alzheimer's disease. Treatment 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. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with aducanumab. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).
Donanemab-azbt (Kisunla®)	For the treatment of Alzheimer's disease. Treatment should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in the clinical trials.
Lecanemab-irmb (Leqembi®)	For the treatment of Alzheimer's disease. Treatment 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.

POSITION STATEMENT:
For Medicare Part B, coverage of the requested drug will be provided in accordance with CMS' National Coverage Determination, Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (200.3), when the policy criteria outlined above are met.[15]

On July 6, 2023, the FDA granted traditional approval to lecanemab. As a result, Medicare broadened its coverage of amyloid targeted therapies to enrolled Medicare members who are diagnosed with mild cognitive impairment or mild Alzheimer's disease dementia with documented evidence of beta-amyloid plaque on the brain. In addition, the medication must be prescribed by a physician who participates in a qualifying registry with an appropriate clinical team and follow-up care.[15, 16] 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). Refer to the CMS Coverage with Evidence Development webpage for approved CED studies: https://www.cms.gov/medicare/coverage-evidence-development/monoclonal-antibodies-directed-against-amyloid-treatment-alzheimers-disease-ad

Cognitive assessments are utilized to evaluate patients presenting with memory loss. Examples of validated cognitive assessments include the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), and the Clinical Dementia Rating (CDR) scale. Please note, not all providers agree on cut-offs for each stage of dementia, so it is important to take into consideration other health exams.

- Mini-Mental Status Exam (MMSE)[17, 18]
    - 30-point scale with items that assess orientation, memory, attention/concentration, language, and visuospatial function. The score relates to the member's level of dementia and are generally grouped as follows:
        - 25 - 30 suggests normal cognition
        - 20 - 24 suggests mild dementia
        - 13 - 20 suggests moderate dementia
        - Less than 12 suggests severe dementia
- Montreal Cognitive Assessment (MoCA)[19]
    - 30-point scale with items that assess delayed word recall, visuospatial/executive function, language, attention/concentration, orientation. Average scores for the following ranges are:
        - Mild Cognitive Impairment: 19 - 25
        - Mild Dementia: 11 - 21
        - Normal: 26 and above
- Clinical Dementia Rating (CDR) Scale [20, 21]
    - 5-point scale that assess memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The score relates to the member's level of dementia:
        - 0 = Normal
        - 0.5 = Very Mild Dementia
        - 1 = Mild Dementia
        - 2 = Moderate Dementia
        - 3 = Severe Dementia

Aducanumab (Aduhelm®)

- In November 2020, the FDA's Peripheral and Central Nervous System Drugs Advisory Committee voted that the results from EMERGE did not provide sufficient evidence to support the effectiveness of aducanumab as a treatment for Alzheimer's disease, and recommended against the approval [3]
- An evidence report released by the Institute for Clinical and Economic Review (ICER) found there is insufficient evidence to determine whether or not aducanumab slows the loss of cognition in patients with Alzheimer's, and there is

uncertainty if it will provide a benefit to patients that would outweigh the potential risks and harms of treatment [4]

- On June 7, 2021, the FDA approved aducanumab (Aduhelm®) for the treatment of Alzheimer's disease. This indication was approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with aducanumab. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials
- On July 8, 2021 the FDA updated the broad indication to specify that treatment should only be initiated in patients with mild forms of Alzheimer's disease as this was the population treated in clinical trials; no safety and effectiveness data is available on initiating treatment in earlier or later stages of the disease than were studied
- Efficacy for aducanumab was evaluated in two, 18-month, double-blind, randomized, placebo controlled, parallel group studies (EMERGE and ENGAGE) in patients with mild cognitive impairment or mild Alzheimer's disease. Both studies were terminated early based on interim analysis showing the trials would not meet their primary endpoints[1,2]
    - Upon subsequent data analysis, it was announced that EMEREGE met the primary endpoint for a subset of patients, while ENGAGE did not.
    - In EMERGE, high-dose aducanumab was associated with statistically significant change from baseline in Clinical Dementia Rating-Sum of Boxes (CDR-SB) compared to placebo at week 78 (treatment difference of -0.39 [-22%], p = 0.0120). Low-dose aducanumab was numerically better than placebo, but the difference was not statistically significant
    - In ENGAGE, no statistically significant difference was observed in the aducanumab treated and placebo-treated patients for the CDR-SB endpoint at week 78
    - A subgroup of patients from EMERGE and ENGAGE were evaluated for changes in key biomarkers using positron emission tomography (PET) and cerebrospinal fluid assays. Individuals receiving high-dose demonstrated significant reductions in beta amyloid plaques compared with placebo
    - The discordant results of these identically designed trials have provided insufficient evidence to support that the lowering of beta amyloid plaque yields a clinical benefit of improved cognition and delayed Alzheimer's disease progression
    - The length of these trials are also insufficient to determine how effective aducanumab is at treating Alzheimer's disease as cognitive decline associated with MCI and mild Alzheimer's disease dementia often spans years

- There are significant safety concerns with aducanumab. The most common adverse events (AEs) included amyloid related imaging abnormalities (ARIA), headache, fall, and diarrhea[1]
    - In the clinical trials ARIA, (brain hemorrhage or brain edema or both) was observed in 41% of patients treated with high dose (10 mg/kg) of aducanumab
    - Approximately one in 10 patients will need to stop treatment due to concerns related to ARIA
    - One patient in the aducanumab arm of an earlier phase trial died of an intracranial hemorrhage determined to be related to study treatment.
    - Per the package label, it is recommended to obtain a recent (within one year) brain magnetic resonance imaging (MRI) prior to initiating treatment followed by subsequent MRI's prior to the 5th, 7th, 9th and 12th infusions
        - ARIA-E
            - For patients with evidence of moderate or severe ARIA-E on MRI, it is recommended to suspend dosing. If there is evidence of mild ARIA-E on MRI but moderate or severe clinical symptoms are present, it is recommended to suspend dosing
        - ARIA-H
            - For patients with evidence of moderate or severe ARIA-H on MRI, dosing should be suspended. If patient is symptomatic, dosing should be suspended regardless of MRI severity

- As of January 2024, the manufacturer of aducanumab, Biogen, announced that it would discontinue the development and commercialization of aducanumab. This decision was not related to safety or efficacy concerns, but rather to reprioritize resources to advance lecanemab. Patients currently prescribed and taking aducanumab will be eligible for continued dosing until November 1, 2024. Aducanumab will no longer be available for purchase after November 1, 2024. [1,6]

Donanaemab (Kisunla®)

- Moderate quality evidence from one phase 3 trial that donanemab may slow disease progression for patients with early Alzheimer's disease based on change in the integrated Alzheimer's Disease Rating Scale (iADRS) score from baseline to 76 weeks.
    - iADRS is a measurement scoring tool that combines scores from the Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-

Cog) and the Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living (ADCS-iADL).
    - The iADRS score falls between 0 to 144, with higher scores indicating greater impairment
    - Clinically meaningful worsening of symptoms is estimated to be 5 points for patients with mild cognitive impairment due to AD and 9 points for patients with AD with mild dementia
  - TRAILBLAZER-ALZ[25]: The change from baseline in the iADRS score at 76 weeks was −6.86 with donanemab and −10.06 with placebo (difference, 3.20; 95% confidence interval, 0.12 to 6.27; P=0.04). In relation to the 144-point scale range, a 3-point change compared to placebo did not meet the minimum clinically important difference (MCID) reported in literature.[26]
  - Dosing of donanemab was continued or stopped in response to observed effects on amyloid imaging. If amyloid plaque level was <11 Centiloids on a single PET scan or 11 to <25 Centiloids on 2 consecutive PET scans, subjects taking donanemab were eligible to switch to placebo. The percentages of patients eligible for switch to placebo based on amyloid PET levels at Week 24, Week 52, and Week 76 timepoints were 17%, 47%, and 69%, respectively.[25]
- Safety[22]
  - Boxed warning: amyloid related imaging abnormalities (ARIA)
    - In TRAILBLAZER ALZ 2 Study, ARIA (symptomatic and asymptomatic events) occurred in 36% of patients treated with donanemab and 14% treated with placebo.
    - Apolipoprotein E4 (ApoE4) homozygous gene carriers have an increased risk of developing ARIA.
    - ARIA can occur at any time, though most events occur early in treatment. It is recommended to obtain a brain magnetic resonance imaging (MRI) prior to initiating treatment followed by subsequent MRI's prior to the 2nd, 3rd, 4th and 7th infusions.
  - Other common adverse effects include headache and infusion related reactions.

Lecanemab (Leqembi®)

- Low quality evidence based on one phase 2b and phase 3 trial that lecanemab may slow disease progression for patients with early Alzheimer's disease
  - Study 201[10]: Accelerated approval based on surrogate endpoint (beta amyloid burden)

        - Lecanemab had a 64% likelihood of 25% or greater slowing of progression on the primary endpoint (change in Alzheimer's Disease Composite Score (ADCOMS)) relative to placebo at 12 months. The primary endpoint, requiring an 80% probability of ≥25% reduction in clinical decline compared to placebo, was not met
        - Key secondary endpoint analysis demonstrated that lecanemab reduced brain amyloid and sustained activity over the 18-month period for several clinical measures
    - CLARITY AD (phase 3)[11]:
        - The change from baseline at 18 months in the primary endpoint (change in Clinical Dementia Rating-Sum of Boxes (CDR-SB)) was less with lecanemab than with placebo, with a difference of 0.45 (95%CI -0.67 to -0.23; p<0.001)
            - Definition of clinically meaningful effects in the primary endpoint are not established. While the difference of 0.45 points between groups on the CDR-SB scale is statistically significant, this may or may not result in a clinically significant change[12, 13]
        - Key secondary endpoints demonstrated greater reduction in brain amyloid burden with lecanemab than with placebo
    - Phase 3 clinical trial demonstrated moderately less decline on cognition and function scales than placebo but was associated with adverse events. At this time it is unknown if these statistically significant results translate to clinically meaningful effects. Longer trials are necessary to determine the efficacy and safety of lecanemab in early Alzheimer's disease
- Institute for Clinical and Economical Review (ICER): Lecanemab for Early Alzheimer's Disease Final Policy Recommendations [14]
    - ICER's report rates treatment with lecanemab in patients with early Alzheimer's disease as "promising but inconclusive"
        - Moderate certainty of a small or substantial net health benefit, small likelihood of a negative net health benefit
        - The net health benefits of lecanemab in patients with early Alzheimer's disease may be small or even substantial, but there remains a possibility of net harm from ARIA
        - Uncertain that targeting amyloid burden is an appropriate surrogate outcome for clinical benefit
        - Cost-effective annual list price range of $8,900 to $21,500
- Safety[7]
    - Warnings and precautions: amyloid related imaging abnormalities (ARIA)

- In Study 201, ARIA (symptomatic and asymptomatic events) occurred in 12% of patients treated with lecanemab and 5% treated with placebo. In CLARITY-AD, ARIA occurred in 21% of patients treated with lecanemab and 9% treated with placebo.
- Apolipoprotein E4 (ApoE4) homozygous gene carriers have an increased risk of developing ARIA
- ARIA can occur at any time, though in clinical trials most events occurred early in treatment (within the first seven doses). It is recommended to obtain a recent (within one year) brain magnetic resonance imaging (MRI) prior to initiating treatment followed by subsequent MRI's prior to the 5th, 7th, and 14th infusions
- ARIA-E
  - For patients with evidence of moderate or severe ARIA-E on MRI, it is recommended to suspend dosing. If there is evidence of mild ARIA-E on MRI but moderate or severe clinical symptoms are present, it is recommended to suspend dosing
- ARIA-H
  - For patients with evidence of moderate or severe ARIA-H on MRI, dosing should be suspended. If patient is symptomatic, dosing should be suspended regardless of MRI severity

- Due to risks of intracerebral hemorrhage with therapy, caution is recommended when considering use of an antithrombotic or a thrombolytic agent (tissue plasminogen activator) in a patient being treated with lecanemab
- Most common adverse effects include infusion related reactions

REFERENCE/RESOURCES:

1. Aduhelm [package insert]. Cambridge, MA; Biogen Inc; 2023 August.
2. Knopman DS, Jones DT, and Greicius MD. Failure to demonstrate efficacy of aducanumab: An analysis of the EMERGE and ENGAGE trials as reported by Biogen, December 2019. Alzheimer's Dement. 2020; 1-6
3. U.S. Food and Drug Administration. Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee – Aducanumab. November 6, 2020. Accessed August 23, 2024. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/aducanumab-marketed-aduhelm-information
4. Lin GA, Whittington MD, Synnott PG, McKenna A, Campbell J, Pearson SD, Rind DM. Aducanumab for Alzheimer's Disease: Effectiveness and Value;

Evidence Report. Institute for Clinical and Economic Review, June 30, 2021. https://icer.org/assessment/alzheimers-disease-2021/.

5. Kuller LH, Lopez OL. ENGAGE and EMERGE: Truth and consequences? Alzheimer's Dement. 2021 Apr;17(4):692-695. doi: 10.1002/alz.12286. Epub 2021 Mar 3. PMID: 33656288.
6. Biogen. Biogen to Realign Resources for Alzheimer's Disease Franchise. Accessed August 23, 2024. https://investors.biogen.com/news-releases/news-release-details/biogen-realign-resources-alzheimers-disease-franchise
7. Leqembi® package insert. Nutley, NJ: Eisai Inc.; 2023 July.
8. Leqembi® In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed June 28, 2024.
9. Leqembi® In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed June 28, 2024.
10. Swanson CJ, Zhang Y, Dhadda S, et al. A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody. Alzheimers Res Ther. 2021 Apr 17;13(1):80. doi: 10.1186/s13195-021-00813-8. Erratum in: Alzheimers Res Ther. 2022 May 21;14(1):70.
11. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease. N Engl J Med 2022 November 29. DOI:10.1056/NEJMoa2212948
12. Lansdall CJ, McDougall F, Butler LM, et al. Establishing Clinically Meaningful Change on Outcome Assessments Frequently Used in Trials of Mild Cognitive Impairment Due to Alzheimer's Disease. J Prev Alzheimers Dis. 2023;10(1):9-18.
13. Andrews JS, Desai U, Kirson NY, et al. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. Alzheimer's Dement (N Y). 2019 Aug 2;5:354-363.
14. Lin GA, Whittington MD, Wright A, Agboola F, Herron-Smith S, Pearson SD, Rind DM. Lecanemab for Early Alzheimer's Disease Final Evidence Report. Institute for Clinical and Economic Review, April 17, 2023.
15. Centers for Medicare & Medicaid Services Medicare Coverage Database. National Coverage Determination: Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (200.3). December 12, 2022. Available at: https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=375&ncdver=1&keyword=amyloid&keywordType=starts&areaId=all&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=1 Accessed June 28, 2024.

16. Centers for Medicare & Medicaid Services. Statement: Broader Medicare Coverage of Leqembi Available Following FDA Traditional Approval. Found on the internet at https://www.cms.gov/newsroom/press-releases/statement-broader-medicare-coverage-leqembi-available-following-fda-traditional-approval
17. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res.1975;12(3):189-98.
18. Tsoi KK, Chan JY, Hirai HW, Wong SY, Kwok TC. Cognitive Tests to Detect Dementia: A Systematic Review and Meta-analysis. JAMA Intern Med. 2015 Sep;175(9):1450-8. doi: 10.1001/jamainternmed.2015.2152. PMID: 26052687.
19. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005 Apr;53(4):695-9. doi: 10.1111/j.1532-5415.2005.53221.x. Erratum in: J Am Geriatr Soc. 2019 Sep;67(9):1991. PMID: 15817019.
20. O'Bryant SE, Waring SC, Cullum CM, et al. Staging dementia using Clinical Dementia Rating Scale Sum of Boxes scores: a Texas Alzheimer's research consortium study. Arch Neurol. 2008;65(8):1091-1095.
21. CDR Dementia Staging Instrument. Knight Alzheimer Disease Research Center. https://knightadrc.wustl.edu/cdr/cdr.htm. Accessed: June 28, 2024.
22. Kisunla (donanemab) Package insert. Indianapolis, IN: Eli Lilly and Company; July 2024.
23. Donanemab In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed August 23, 2024.
24. Donanemab In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed August 23, 2024.
25. Sims JR, et al. Donanemab in early symptomatic Alzheimer disease: The TRAILBLAZER-ALZ 2 randomized clinical trial. JAMA. 2023;330(6):512–527.
26. Wessels AM, et al. Meaningful clinical changes in Alzheimer disease measured with the iADRS and illustrated using the donanemab TRAILBLAZER-ALZ study findings. Neurol Clin Pract. 2023;13(2):e200127

Table 2: Dosing and ARIA Monitoring

Drug	MRI Timing for ARIA Monitoring	Dosing	Frequency of Administration
Aducanumab	Prior to Infusion 1	See Prescribing Information for dosing recommendations and for interruptions in therapy due to ARIA	Every 4 weeks
	Prior to Infusion 5		
	Prior to Infusion 7		
	Prior to Infusion 9		
	Prior to Infusion 12		
Donanemab	Prior to Infusion 1		Every 4 weeks
	Prior to Infusion 2		
	Prior to Infusion 3		
	Prior to Infusion 4		
	Prior to Infusion 7		
Lecanemab	Prior to Infusion 1		Every 2 weeks
	Prior to Infusion 5		
	Prior to Infusion 7		
	Prior to Infusion 14		

ARIA = amyloid related imaging abnormalities; IV = intravenous; MRI = magnetic resonance imaging

Appendix 1. Billing Code

HCPCS Code	Drug	Billable Units
J0172	Injection, aducanumab-avwa, 2 mg	1 billable unit = 2 mg
J0175	Injection, donanemab-azbt, 2mg	1 billable unit = 2 mg
J0174	Injection, lecanemab-irmb, 1 mg	1 billable unit = 1 mg