Kisunla™ (Donanemab-Azbt)

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➲ Instructions for Use

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Related Community Plan Policy

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

Coverage Rationale

Kisunla (donanemab-azbt) has been added to the Review at Launch program. Some members may not be eligible for coverage of this medication at this time. Refer to the Medical Benefit Drug Policy titled Review at Launch for New to Market Medications for additional details.

Kisunla (donanemab-azbt) 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:[15, 16, 24, 38]
    - Mild cognitive impairment (MCI) due to Alzheimer's disease; **or**
    - Mild dementia due to Alzheimer's disease;

    and
  - Submission of medical records (e.g., chart notes, laboratory values) documenting **all** of the following:[31,42-44]
    - 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 20 or greater
      - Montreal Cognitive Assessment (MoCA) score of 17 or greater
      - Saint Louis University Mental Status (SLUMS) 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 positive amyloid positron emission tomography (PET) brain scan; **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:[38]
      - Patient is currently taking an anticoagulant (e.g., warfarin, dabigatran); **and**
      - Counseling has been provided that the combined use of Kisunla with anti-coagulant drugs may increase the risk of cerebral macrohemorrhage and prescriber attests that the patient has shared in decision-making to initiate Kisunla therapy

    and
  - Patient has no history of intracerebral hemorrhage 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 Kisunla; **and**
  - Testing for ApoE ε4 status has been offered to the patient and prescriber attests that the patient has shared in decision-making to initiate Kisunla 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 Aβ monoclonal antibodies (mAbs) for Alzheimer's Disease (e.g., Aduhelm, Leqembi); **and**
- Prescribed by a neurologist, geriatric psychiatrist, or geriatrician who specializes in treating dementia; **and**
- Kisunla 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:
    - Mild cognitive impairment (MCI) due to Alzheimer's disease; **or**
    - Mild dementia due to Alzheimer's disease;

    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):
    - 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 20 or greater
      - Montreal Cognitive Assessment (MoCA) score of 17 or greater
      - Saint Louis University Mental Status (SLUMS) score of 17 or greater

    and
  - **One** of the following:
    - **Both** of the following:
      - Patient has received Kisunla therapy for less than or equal to 6 months; **and**
      - **One** of the following:
        - A post-treatment amyloid PET brain scan performed < 1 month prior to request for continued treatment is positive for amyloid based on visual read; **or**
        - Prescriber attests that amyloid PET imaging will be performed prior to 18 months of total treatment to assess for the effect of Kisunla treatment on amyloid plaque;

      or
    - **Both** of the following:
      - Patient has received Kisunla therapy for greater than 6 months; **and**
      - **Both** of the following:
        - A post-treatment amyloid PET brain scan obtained between 12 and 18 months of total treatment is positive for amyloid based on visual read; **and**
        - For treatment beyond 18 months of therapy, a post-treatment amyloid PET brain scan is performed at least once per 12 months and is positive for amyloid based on visual read;

    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**
    - **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 Kisunla 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 Kisunla is appropriate based on the radiographic severity of ARIA

and

- Not used in combination with other Aβ monoclonal antibodies (mAbs) for Alzheimer's Disease (e.g., Aduhelm, Leqembi); **and**
- Prescribed by a neurologist, geriatric psychiatrist, or geriatrician who specializes in treating dementia; **and**
- Kisunla dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
- Reauthorization is for no more than 12 months

Kisunla (donanemab-azbt) 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.

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
J0175	Injection, donanemab-azbt, 2mg

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 cases.[1] 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 amyloid-beta Aβ plaques and neurofibrillary tangles (comprised of abnormal tau protein) in the brain, accompanied by synaptic dysfunction and neurodegeneration.[3,4] The deposition of Aβ (as amyloid plaques) generally begins decades before any symptoms of AD are observed. More specifically, Aβ 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 Aβ plaque core, and in the neuropil as neuropil threads.[6]

There are two ways to detect abnormal Aβ, either directly via PET imaging using tracers or indirectly by measuring the levels of the long form of Aβ 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 Aβ 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 ≥ 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 (ε4) allele has been confirmed to be an important risk factor for AD in many clinical trials.
- Factors that may influence the impact of APOE ε4 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.[18,31] 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.[18]

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.[8,9,19,31]

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.[8,32]

The Integrated Alzheimer's Disease Rating Scale (iADRS) is a linear combination of its two components: the ADAS-Cog13 and the Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living scale (ADCS-iADL) (range: 0–59; lower scores indicating greater impairment; items: 6a and 7–23). Because worse outcomes are indicated by higher scores on the ADAS-Cog13 and lower scores on the ADCS-iADL, the ADAS-Cog13 score is multiplied by −1 when calculating the iADRS score, such that lower iADRS scores indicate greater impairment. iADRS scores range from 0 to 144. The minimal clinically important difference of the iADRS has been suggested to be 5 points for MCI due to AD and 9 points for AD with mild dementia.[45]

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 National Institute on Aging and the Alzheimer's Association (NIA-AA) research framework committee created a numeric clinical staging scheme applicable for diagnosing those in the Alzheimer's continuum. The six-stage numeric clinical staging scheme was brought forward largely unchanged (table below) into an Alzheimer's Association 2024 revision of the 2018 framework.[46]

Stage	Numeric Clinical Staging–Applicable Only to Individuals in the Alzheimer's Disease Continuum
Stage 0 Asymptomatic, deterministic gene	• No evidence of clinical change. Biomarkers in normal range.
Stage 1 Asymptomatic, biomarker evidence only	• Performance within expected range on objective cognitive tests. • No evidence of recent cognitive decline or new symptoms.

Stage	Numeric Clinical Staging–Applicable Only to Individuals in the Alzheimer's Disease Continuum
Stage 2 Transitional decline: mild detectable change, but minimal impact on daily function	• Normal performance within expected range on objective cognitive tests. • Decline from previous level of cognitive or neurobehavioral function that represents a change from individual baseline within the past 1 to 3 years, and has been persistent for at least 6 months. • May be documented by evidence of subtle decline on longitudinal cognitive testing, which may involve memory or other cognitive domains but performance still within normal range. • May be documented through subjective report of cognitive decline. • May be documented with recent-onset change in mood, anxiety, motivation not explained by life events. • Remains fully independent with no or minimal functional impact on activities of daily living (ADLs).
Stage 3 Cognitive impairment with early functional impact	• 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 assessments. • Performs daily life activities independently, but cognitive difficulty may result in detectable functional impact on complex ADLs (i.e., may take more time or be less efficient but still can complete—either self-reported or corroborated by an observer).
Stage 4 Dementia with mild functional impairment	• Progressive cognitive and mild functional impairment on instrumental ADLs, with independence in basic ADLs.
Stage 5 Dementia with moderate functional impairment	• Progressive cognitive and moderate functional impairment on basic ADLs requiring assistance.
Stage 6 Dementia with severe functional impairment	• Progressive cognitive and functional impairment, and complete dependence for basic ADLs.

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. Cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) and the NMDA-antagonist, memantine, are the only FDA-approved and guideline-recommended treatments for AD dementia.[10] 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.[9]

Kisunla (donanemab-azbt) is a humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against insoluble N-truncated pyroglutamate amyloid beta. The accumulation of amyloid beta plaques in the brain is a defining pathophysiological feature of Alzheimer's disease. Donanemab-azbt reduces amyloid beta plaques.

Clinical Evidence

Multiple investigational anti-Aβ antibodies have been developed with the goal of either reducing production of Aβ or lowering levels of aggregated Aβ 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-Aβ antibodies include the following:[5,14]

- Inclusion of patients in clinical trials without evidence of Aβ pathology
- Unknown or no target engagement prior to initiation of Phase 3 study (i.e., poor selectivity of drug for neurotoxic Aβ)

- Lack of robust and sustained inhibition of soluble Aβ 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

FDA approval for donanemab was based on TRAILBLAZER-ALZ 2, a double-blind, placebo-controlled, parallel-group study (Study 1, NCT04437511) in patients with Alzheimer's disease (patients with confirmed presence of amyloid pathology and mild cognitive impairment or mild dementia stage of disease, consistent with Stage 3 and Stage 4 Alzheimer's disease). Patients were enrolled with a Mini-Mental State Examination (MMSE) score of ≥ 20 and ≤ 28 and had a progressive change in memory function for at least 6 months. Patients were included in the study based on visual assessment of tau PET imaging with flortaucipir and standardized uptake value ratio (SUVR). Patients were enrolled with or without concomitant approved therapies (cholinesterase inhibitors and the N-methyl-D-aspartate antagonist memantine) for Alzheimer's disease. Patients could enroll in an optional, long-term extension. In TRAILBLAZER-ALZ 2, 1736 patients were randomized 1:1 to receive 700 mg of donanemab every 4 weeks for the first 3 doses, and then 1400 mg every 4 weeks (N = 860) or placebo (N = 876) for a total of up to 72 weeks. The treatment was switched to placebo based on amyloid PET levels measured at Week 24, Week 52, and Week 76. If the amyloid plaque level was < 11 Centiloids on a single PET scan or 11 to < 25 Centiloids on 2 consecutive PET scans, the patient was eligible to be switched to placebo. Additionally, dose adjustments were allowed for treatment-emergent ARIA or symptoms that then showed ARIA-E or ARIA-H on MRI. At baseline, mean age was 73 years, with a range of 59 to 86 years. Of the total number of patients randomized, 68% had low/medium tau level and 32% had high tau level; 71% were ApoE ε4 carriers and 29% were ApoE ε4 noncarriers. Fifty-seven percent of patients were female, 91% were White, 6% were Asian, 4% were Hispanic or Latino, and 2% were Black or African American. The primary efficacy endpoint was change in the integrated Alzheimer's Disease Rating Scale (iADRS) score from baseline to 76 weeks. The iADRS is a combination of two scores: the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog13) and the Alzheimer's Disease Cooperative Study – instrumental Activities of Daily Living (ADCS-iADL) scale. The total score ranges from 0 to 144, with lower scores reflecting worse cognitive and functional performance. Other efficacy endpoints included Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB), ADAS-Cog13, and ADCS-iADL. There were two primary analysis populations based on tau PET imaging with flortaucipir: 1) low/medium tau level population (defined by visual assessment and SUVR of ≥ 1.10 and ≤ 1.46), and 2) combined population of low/medium plus high tau (defined by visual assessment and SUVR >1.46) population. Patients treated with donanemab demonstrated a statistically significant reduction in clinical decline on iADRS compared to placebo at Week 76 in the combined population (difference, 2.92 [95% CI, 1.51-4.33]; P < .001) and the low/medium tau population (difference, 3.25 [95% CI, 1.88-4.62]; P < .001). Patients treated with donanemab demonstrated a statistically significant reduction in clinical decline on CDR-SB compared to placebo at Week 76 in the combined population (difference, −0.7 [95% CI, −0.95 to −0.45]; P < .001). There were also statistically significant differences (P < 0.001) between treatment groups as measured by ADAS-Cog13 and ADCS-iADL at Week 76. Dosing was continued or stopped in response to observed effects on amyloid imaging. 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. Amyloid PET values may increase after treatment with donanemab is stopped. There is no data beyond the 76-week duration of TRAILBLAZER-ALZ 2 to guide whether additional dosing with donanemab may be needed for longer-term clinical benefit.

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.

Kisunla (donanemab-azbt) is indicated for the treatment of Alzheimer’s disease. Treatment with Kisunla 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.

References

1. Alzheimer's Association. 2024 Alzheimer's disease facts and figures. https://www.alz.org/media/documents/alzheimers-facts-and-figures.pdf. Accessed August 5, 2024.
2. Arvanitakis Z, Shah RC, Bennett DA. Diagnosis and management of dementia: a review. JAMA. 2019;322(16):1589-1599.
3. Hyman BT, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer’s Association guidelines for the neuropathic assessment of Alzheimer’s disease. Alzheimer’s Dement. 2012;8(1):1-13.

4. Iqbal K, Liu F, Gong CX, et al. Tau in Alzheimer's Disease and related tauopathies. Curr Alzheimer Res. 2010;7(8): 656–664.
5. Wolk DA, Dickerson BC. Clinical features and diagnosis of Alzheimer disease. UpToDate Web site. Updated October 8, 2021. http://www.uptodate.com. Accessed August 5, 2024.
6. Keene CD, Montine TJ, Kuller LH. Epidemiology, pathology, and pathogenesis of Alzheimer disease. UpToDate Web site. Updated August 23, 2022. http://www.uptodate.com. Accessed August 5, 2024.
7. Sherva R, Kowall NW. Genetics of Alzheimer disease. UpToDate Web site. Updated May 19, 2022. http://www.uptodate.com. Accessed August 5, 2024.
8. O'Bryant SE, Lacritz LH, Hall LH, et al. Validation of the new interpretive guidelines for the clinical dementia rating scale sum of boxes score in the National Alzheimer's Coordinating Center database. Arch Neurol. 2010;67(6):746-749.
9. Press D, Alexander A. Cholinesterase inhibitors in the treatment of dementia. UpToDate Web site. Updated May 28, 2024. http://www.uptodate.com. Accessed August 5, 2024.
10. Atri A. The Alzheimer's disease clinical spectrum diagnosis and management. Med Clin N Am. 2019;103:263-293.
11. Tolar M, Abushakra S, Sabbagh M. The path forward in Alzheimer's disease therapeutics: Reevaluating the amyloid cascade hypothesis. Alzheimers Dement. 2020;16(11):1553-1560.
12. Clinicaltrials.gov Web site. https://clinicaltrials.gov/study/NCT03367403. Accessed August 5, 2024.
13. Petersen RC, Lopez O, Armstrong MJ, et al. Practice guideline update: mild cognitive impairment. Neurology. 2018;90(3):126-135.
14. ClinicalTrials.gov: https://clinicaltrials.gov/study/NCT04437511. Accessed August 5, 2024.
15. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):263-269.
16. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):270-279.
17. ClinicalTrials.gov: https://clinicaltrials.gov/study/NCT05026866. Accessed August 5, 2024.
18. 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.
19. 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):189-198.
20. Hanssona O, Seibylc J, Stomruda E, et al. CSF biomarkers of Alzheimer's disease concord with amyloid-β PETand predict clinical progression: A study of fully automated immunoassays in BioFINDER and ADNI cohorts. Alzheimers Dement. 2018 November; 14(11): 1470–1481. Supplementary data related to this article can be found at https://doi.org/10.1016/j.jalz.2018.01.010.
21. S.-K. Herukka et al. Recommendations for cerebrospinal fluid Alzheimer's disease biomarkers in the diagnostic evaluation of mild cognitive impairment. Alzheimer's & Dementia 13 (2017) 285-295. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jalz.2016.09.009.
22. Alcolea D, et al. Agreement of amyloid PET and CSF biomarkers for Alzheimer's disease on Lumipulse. Annals of Clinical and Translational Neurology 2019; 6(9): 1815-1824.
23. MayoCliniclabs.com: ADEVL - Clinical: Alzheimer Disease Evaluation, Spinal Fluid. https://www.mayocliniclabs.com/test-catalog/Overview/607273. Accessed August 5, 2024.
24. Jack CR Jr, Bennett DA, Blennow K, et al: NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement. 2018 Apr;14(4):535-562.
25. Lifke V, Kollmorgen G, Manuilova E, et al: Elecsys Total-Tau and Phospho-Tau (181P) CSF assays: Analytical performance of the novel, fully automated immunoassays for quantification of tau proteins in human cerebrospinal fluid. Clin Biochem. 2019 Oct;72:30-38.
26. Willemse EAJ, van Maurik IS, Tijms BM, et al: Diagnostic performance of Elecsys immunoassays for cerebrospinal fluid Alzheimer's disease biomarkers in a nonacademic, multicenter memory clinic cohort: The ABIDE project. Alzheimers Dement (Amst). 2018 Sep 12;10:563-572.

27. Hansson O, Seibyl J, Stomrud E et al: CSF biomarkers of Alzheimer's disease concord with amyloid-beta PET and predict clinical progression: A study of fully automated immunoassays in BioFINDER and ADNI cohorts. Alzheimers Dement. 2018 Nov;14(11):1470-1481.
28. Schindler SE, Gray JD, Gordon BA, et al: Cerebrospinal fluid biomarkers measured by Elecsys assays compared to amyloid imaging. Alzheimers Dement. 2018 Nov;14(11):1460-1469.
29. Shaw LM, Arias J, Blennow K, et al: Appropriate use criteria for lumbar puncture and cerebrospinal fluid testing in the diagnosis of Alzheimer's disease. Alzheimers Dement. 2018; 14(11):1505-1521.
30. Hansson O, Batrla R, Brix B, et al: The Alzheimer's Association international guidelines for handling of cerebrospinal fluid for routine clinical measurements of amyloid beta and tau. Alzheimers Dement. 2021 Mar 31. doi: 10.1002/alz.12316. Epub ahead of print.
31. Andrews JS, et al: Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. Alzheimer's & Dementia: Translational Research & Clinical Interventions 5 (2019) 354-363.
32. Schrag A, Schott JM; Alzheimer's Disease Neuroimaging Initiative. What is the clinically relevant change on the ADAS-Cog? J Neurol Neurosurg Psychiatry. 2012 Feb;83(2):171-3.
33. Mendez MF. Mental status scales to evaluate cognition. UpToDate Website. Updated April 14, 2023. http://www.uptodate.com. Accessed August 5, 2024.
34. Minoshima S, Drzezga AE, Barthel H, et al. SNMMI Procedure Standard/EANM Practice Guideline for Amyloid PET Imaging of the Brain 1.0. J Nucl Med. 2016 Aug;57(8):1316-22.
35. Clinicaltrials.gov Web site. https://clinicaltrials.gov/study/NCT05108922. Accessed August 5, 2024.
36. Clinicaltrials.gov Web site. https://clinicaltrials.gov/study/NCT05508789. Accessed August 5, 2024.
37. Mintun MA, Lo AC, Duggan Evans C, et al. Donanemab in Early Alzheimer's Disease. N Engl J Med. 2021;384(18):1691-1704. doi:10.1056/NEJMoa2100708.
38. Kisunla [Package insert]. Eli Lilly and Company. Indianapolis, IN. July 2024.
39. Clinicaltrials.gov Web site. https://clinicaltrials.gov/study/NCT05738486. Accessed August 5, 2024.
40. Clinicaltrials.gov Web site. https://clinicaltrials.gov/study/NCT04640077. Accessed August 5, 2024.
41. Sims JR, Zimmer JA, Evans CD, et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA. 2023;330(6):512-527. doi:10.1001/jama.2023.13239.
42. Lansdall CJ, McDougall F, Butler LM, Delmar P, Pross N, Qin S, McLeod L, Zhou X, Kerchner GA, Doody RS. 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. doi: 10.14283/jpad.2022.102. PMID: 36641605.
43. Cedarbaum JM, Jaros M, Hernandez C, Coley N, Andrieu S, Grundman M, Vellas B; Alzheimer's Disease Neuroimaging Initiative. Rationale for use of the Clinical Dementia Rating Sum of Boxes as a primary outcome measure for Alzheimer's disease clinical trials. Alzheimers Dement. 2013 Feb;9(1 Suppl):S45-55. doi: 10.1016/j.jalz.2011.11.002. Epub 2012 Jun 1. PMID: 22658286.
44. Coley N, Andrieu S, Jaros M, Weiner M, Cedarbaum J, Vellas B. Suitability of the Clinical Dementia Rating-Sum of Boxes as a single primary endpoint for Alzheimer's disease trials. Alzheimers Dement. Nov 2011;7(6):602-610 e2. doi:10.1016/j.jalz.2011.01.005.
45. Wessels AM, Rentz DM, Case M, Lauzon S, Sims JR. Integrated Alzheimer's Disease Rating Scale: Clinically meaningful change estimates. Alzheimers Dement (N Y). 2022 Jun 6;8(1):e12312. doi: 10.1002/trc2.12312. PMID: 35676941; PMCID: PMC9169866.
46. Jack CR Jr, Andrews JS, Beach TG, Buracchio T, Dunn B, Graf A, Hansson O, Ho C, Jagust W, McDade E, Molinuevo JL, Okonkwo OC, Pani L, Rafii MS, Scheltens P, Siemers E, Snyder HM, Sperling R, Teunissen CE, Carrillo MC. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. Alzheimers Dement. 2024 Jun 27. doi: 10.1002/alz.13859. Epub ahead of print. PMID: 38934362.

Policy History/Revision Information

Date	Summary of Changes
11/01/2024	• New Medical Benefit Drug Policy

Instructions for Use

This Medical Benefit Drug 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 Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.