BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

ZUNVEYL (benzgalantamine) delayed-release tablet Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and/or Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Medical Necessity Requirements for ZUNVEYL (benzgalantamine)

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by a physician specializing in dementia diagnosis or in consultation with a Neurologist

Indication
- Mild to moderate dementia of the Alzheimer's type

Age Requirement
- 18 years or older

ORIGINAL EFFECTIVE DATE: 05/15/2025 | ARCHIVE DATE: | LAST REVIEW DATE: 05/21/2026 | LAST CRITERIA REVISION DATE:

PHARMACY COVERAGE GUIDELINE

ZUNVEYL (benzgalantamine) delayed-release tablet Generic Equivalent (if available)

Baseline Clinical Evaluation

- Completed **TWO** of the following:
  - Diagnosis confirmed using National Institute of Neurological and Communicative Disorders and Stroke Alzheimer's Disease and Related Disorders Association (NINCDS ADRDA) criteria
  - Mini Mental State Examination scores between 10 and 24 (inclusive)
  - Diagnostic and Statistical Manual of Mental Disorders (DSM) 5th edition criteria for dementia

Alternative Therapies

- Failure, contraindication, intolerance to **ALL** the following:
  - Donepezil
  - Galantamine
  - Rivastigmine
  - Memantine

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No concomitant drug use that may cause severe adverse reaction or significant drug interaction
- No known hypersensitivity to benzgalantamine, galantamine, or any inactive ingredients in Zunveyl
- No severe hepatic impairment (Child Pugh score 10 to 15)
- No creatinine clearance less than 9 mL/min

Documentation Requirements

- A completed request form must be submitted including:
  - Chart notes
  - Lab results (Mini Mental State Examination scores, creatinine clearance, hepatic function)
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration

- 6 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy):

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

Prescriber Qualifications

- Continues to be seen by a physician specializing in dementia diagnosis or in consultation with a Neurologist

PHARMACY COVERAGE GUIDELINE

ZUNVEYL (benzgalantamine) delayed-release tablet Generic Equivalent (if available)

Clinical Response

- Achieved and maintains a 4 point change on the ADAS Cog over baseline
- Functionality retained in most activities of daily living

Adherence

- Adherence to the prescribed therapy regimen has been documented

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No development of contraindications or significant adverse drug effects such as severe skin rash (e.g., Stevens Johnson syndrome, acute generalized exanthematous pustulosis)
- No concomitant drug use that may cause severe adverse reaction or significant drug interaction
- No severe hepatic impairment (Child Pugh score 10 to 15)
- No creatinine clearance less than 9 mL/min

Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement in dementia symptoms
- Lab values confirming safe continued use

Continuation Therapy Criteria Approval Duration

- 12 months OR end of plan year

Criteria for Off-Label Use Requests:

Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. Off-Label Use of Non-Cancer Medications

2. Off-Label Use of Cancer Medications

Description:

Zunveyl (benzgalantamine) is a cholinesterase inhibitor indicated for the treatment of mild to moderate dementia of the Alzheimer's type in adults. Benzgalantamine is a prodrug of galantamine, an acetylcholinesterase inhibitor. Systemic exposures of benzgalantamine are less than 1% of galantamine exposures. The safety of Zunveyl has been established in studies of galantamine immediate release tablets and galantamine extended-release

capsules. The efficacy of Zunveyl is based upon 3 bioavailability studies in healthy adults comparing galantamine immediate-release tablets and galantamine extended-release capsules to Zunveyl. Zunveyl was approved by the FDA via the 505(b)(2) regulatory pathway, based on previously established safety and efficacy for galantamine hydrobromide.

The effectiveness of galantamine as a treatment for Alzheimer's disease is demonstrated by the results of 5 randomized, double-blind, placebo-controlled clinical investigations in patients with probable Alzheimer's disease, 4 with the immediate-release tablet and 1 with the extended-release capsule. Individuals were diagnosed by NINCDS-ADRDA criteria, with Mini-Mental State Examination (MMSE) scores that were ≥10 and ≤24. Doses studied with the immediate-release tablet were 8-32 mg/day given as twice daily doses.

In each study, the primary effectiveness of galantamine was evaluated using a dual outcome assessment strategy as measured by the Alzheimer's Disease Assessment Scale (ADAS-cog) and the Clinician's Interview Based Impression of Change that required the use of caregiver information (CIBIC-plus). The CIBIC-plus is not a single instrument and is not a standardized instrument like the ADAS-cog.

Although the etiology of cognitive impairment in Alzheimer's disease (AD) is not fully understood, it has been reported that acetylcholine-producing neurons degenerate in the brains of patients with Alzheimer's disease. The degree of this cholinergic loss has been correlated with degree of cognitive impairment and density of amyloid plaques (a neuropathological hallmark of Alzheimer's disease).

Galantamine, a tertiary alkaloid, is a competitive and reversible inhibitor of acetylcholinesterase. While the precise mechanism of galantamine's action is unknown, it is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by cholinesterase. If this mechanism is correct, galantamine's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that galantamine alters the course of the underlying dementing process.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Alzheimer's Disease Assessment Scales (ADAS)
https://pmc.ncbi.nlm.nih.gov/articles/PMC5929311/#:~:text=DEVELOPMENT%20OF%20THE%20ALZHEIMER'S%20DISEASE,%2C%20and%20Language%20%5B17%5D.

ADAS is a widely used clinical tool for evaluating the severity of cognitive and behavioral symptoms in Alzheimer's disease (AD)

Purpose:

To assess the progression of AD
To monitor treatment effectiveness
To detect early signs of cognitive decline

Components:

The full ADAS consists of two subscales:

- **ADAS-Cog (Cognitive Subscale):**

Measures cognitive domains such as memory, language, orientation, and praxis

- **ADAS-Noncog (Non-Cognitive Subscale):**
  Assesses behavioral changes, mood disturbances, and activities of daily living

Scoring:

- Each item on the ADAS-Cog and ADAS-Noncog is scored, higher scores indicate greater impairment
- The total ADAS-Cog score ranges from 0 to 70, and the total ADAS-Noncog score ranges from 0 to 50

Interpretation:

- Higher scores on both subscales indicate more severe cognitive and behavioral impairments
- Cut-off points for diagnosing AD may vary, but a score of 18 or higher on the ADAS-Cog is generally considered indicative of significant cognitive impairment
- A 4-point change on the ADAS-Cog at 6 months is often considered a clinically important difference

Advantages:

- Widely used and well-established
- Sensitive to changes in cognitive function
- Provides a comprehensive assessment of cognitive and behavioral symptoms

Limitations:

- Not a diagnostic tool itself
- Can be subjective and influenced by rater bias
- May not be suitable for individuals with severe cognitive impairment

Other Considerations:

- There are several variations of the ADAS, including the ADAS-Cog 11, ADAS-Cog 5, ADAS-ADL, others
- The ADAS is often used in conjunction with other cognitive assessments, such as the Mini-Mental State Examination (MMSE)

It's important to note that the ADAS should be administered and interpreted by a qualified healthcare professional

ADAS-Cog 11 Tasks		
Task	Description	Scoring
Word Recall	A list of 10 words is read by the subject, and then the subject is asked to verbally recall as many of the words as possible. Three trials of reading and recalling are performed	Mean number of words not recalled across the three trials; scoring range is 0 to 10 [Note: An informative task for assessing cognitive ability in mild cognitive impairment (MCI)]
Word Recognition	The subject reads 12 words aloud, and then these twelve words are randomly shuffled with 12 new words, and the subject is asked whether they have previously seen each of the 24 words. Three trials are performed	Mean number of correct responses across the three trials; scoring range is 0 to 12 [Note: An informative task for assessing cognitive ability in MCI]
Naming Objects and Fingers	The subject is asked to name the fingers of their dominant hand as well as 12 objects: flower (plastic), bed (doll house furniture), whistle, pencil, rattle, mask, scissors, comb, wallet, harmonica, stethoscope, and tongs	The number of fingers and objects correctly named; scoping range is 0 to 4

		[Note: An informative task for assessing cognitive ability in MCI]
Orientation	The subject is asked the date, month, year, day of the week, season, time of day, place, and person	The number of correct responses; scoring range is 0 to 8 [Note: An informative task for assessing cognitive ability in MCI]
Remembering Test Instructions	The administrator provides an assessment according to the number of times that the subject needed to be reminded of instructions for the Word Recognition task	The administrator provides a score from 1 to 5
Commands	The subject is asked to perform commands that involve 1-5 steps. For example, the 2-step command is to "Point to the ceiling, then to the floor"	Scored from 0 to 5 based on the largest number of steps that are correctly performed (score is 0 if five step command is correctly performed)
Language	After the administration of the Word Recall task (Q1) ten minutes of open-ended conversation occur between the test administrator and subject, before the remainder of the tasks are presented. These ten minutes of conversation are used to assess language ability.	Quality of speech is given a global rating by the administrator that ranges from 0 to 5
Ideational Praxis (i.e., ability to perform skilled movements)	The subject is asked to pretend to send a letter to themselves: fold letter, put letter in envelope, seal envelope, address envelope, and put a stamp on the envelope	Scored from 0 to 5 based on difficulty of performing the five components
Constructional Praxis (i.e., ability to perform skilled movements)	The subject is shown four geometric forms (circle, two overlapping rectangles, rhombus, cube) and asked to copy them on a piece of paper	Scored from 0 to 5 based on the number of correctly drawn forms
Comprehension of Spoken Language	This task also relies on the ten minutes of open-ended conversation. The administrator provides an assessment of how well the subject can understand speech	The administrator provides a score from 0 to 5
Word Finding Difficulty	During the aforementioned open-ended conversation, the administrator assesses how much difficulty the subject has in finding desired words	The administer provides a score from 0 to 5
• Overall, ADAS-Cog seems able to provide a measure of disease severity in pre-dementia syndromes • Subjects with AD have the largest change in scores, followed by those with MCI, then those with normal cognition (NC) • Important treatment targets of antidementia drugs that are not assessed by the ADAS-Cog: attention and concentration, planning and executive function, verbal memory, nonverbal memory, and praxis • Ability to perform activities of daily living (ADL) relies upon intact executive function along with other cognitive abilities is now considered an important component of disease severity		

<u>Activities of daily living (ADL)</u>:

Instrumental ADL:

Prepare meals, shop for groceries or clothes, use the telephone, manage money, etc.
Self-care ADL:
Bathe, dress and undress, feed self, use the toilet, take medications, not bedridden

National Institute of Neurological and Communicative Disorders and Stroke (NINCDS)-Alzheimer's Disease and Related Disorders Association (ADRDA)

Diagnostic criteria for AD:

***Probable AD*: "A" plus one or more supportive features B, C, D, or E**

Core diagnostic criteria

A. Presence of an early and significant episodic memory impairment that includes the following features:
1. Gradual and progressive change in memory function reported by patients or informants over more than 6 months
2. Objective evidence of significantly impaired episodic memory on testing: this generally consists of recall deficit that does not improve significantly or does not normalize with cueing or recognition testing and after effective encoding of information has been previously controlled
3. The episodic memory impairment can be isolated or associated with other cognitive changes at the onset of AD or as AD advances

Supportive features

B. Presence of medial temporal lobe atrophy
• Volume loss of hippocampi, entorhinal cortex, amygdala evidenced on MRI with qualitative ratings using visual scoring (referenced to well characterized population with age norms) or quantitative volumetry of regions of interest (referenced to well characterized population with age norms)

C. Abnormal cerebrospinal fluid biomarker
• Low amyloid beta1–42 concentrations, increased total tau concentrations, or increased phospho-tau concentrations, or combinations of the three
• Other well validated markers to be discovered in the future

D. Specific pattern on functional neuroimaging with PET
• Reduced glucose metabolism in bilateral temporal parietal regions
• Other well validated ligands, including those that foreseeably will emerge such as Pittsburg compound B or FDDNP

E. Proven AD autosomal dominant mutation within the immediate family

Exclusion criteria

History
• Sudden onset
• Early occurrence of the following symptoms: gait disturbances, seizures, behavioral changes

Clinical features
• Focal neurological features including hemiparesis, sensory loss, visual field deficits
• Early extrapyramidal signs

Other medical disorders severe enough to account for memory and related symptoms
• Non-AD dementia
• Major depression
• Cerebrovascular disease
• Toxic and metabolic abnormalities, all of which may require specific investigations
• MRI FLAIR or T2 signal abnormalities in the medial temporal lobe that are consistent with infectious or vascular insults

***Definite AD*:**

AD is considered definite if the following are present:

• Both clinical and histopathological (brain biopsy or autopsy) evidence of the disease, as required by the NIA-Reagan criteria for the post-mortem diagnosis of AD; criteria must both be present
• Both clinical and genetic evidence (mutation on chromosome 1, 14, or 21) of AD; criteria must both be present

Diagnostic and Statistical Manual of Mental Disorders (DSM)-5th Edition:

DSM-5 criteria for major neurocognitive disorder (previously dementia)
A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains*: - Learning and memory - Language - Executive function - Complex attention - Perceptual-motor - Social cognition
B. The cognitive deficits interfere with independence in everyday activities. At a minimum, assistance should be required with complex instrumental activities of daily living, such as paying bills or managing medications
C. The cognitive deficits do not occur exclusively in the context of a delirium
D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia)
* Evidence of decline is based on concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function and a substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment

Resources:

Zunveyl (benzgalantamine) delayed-release tab product information, revised by Alpha Cognition, Inc. 07-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 12, 2026.

Kueper JK, Speechly M, Montero-Odasso M. The Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog): Modifications and Responsiveness in Pre-Dementia Populations. A Narrative Review. J Alzheimer's Dis. 2018 Apr 24;63(2):423–444. doi: 10.3233/JAD-170991. Assessed April 02, 2025. Re-evaluated March 27, 2026.

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. Alzheimer's & Dementia 2011 May; 7(3):263-269. doi:10.1016/j.jalz. 2011.03.005. Accessed April 04, 2025. Re-evaluated March 27, 2026.

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. Alzheimer's & Dementia 2011 May; 7(3):273-279. doi:10.1016/j.jalz. 2011.03.008. Accessed April 04, 2025. Re-evaluated March 27, 2026.

Dubois B, Feldman HH, Jacova C, et al.: Research criteria for the diagnosis of Alzheimer's disease revising the NINCDS-ADRDA criteria. Lancet Neurol 2007 Aug; 6 (8): 734–46. Accessed April 03, 2025. Re-evaluated March 27, 2026.

Wolk DA, Dickerson BC. Clinical features and diagnosis of Alzheimer's disease. In: UpToDate, DeKosky ST, Wilterdink JL (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through February 2026. Topic last updated September 30, 2024. Accessed March 27, 2026.

Press D, Buss SS. Treatment of Alzheimer's disease. In: UpToDate, DeKosky ST, Schmader KE, Wilterdink JL (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through February 2026. Topic last updated March 23, 2026. Accessed March 27, 2026.

Press D, Buss SS. Cholinesterase inhibitors in the treatment of dementia. In: UpToDate, DeKosky ST, Schmader KE, Wilterdink JL, Givens J (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through February 2026. Topic last updated June 18, 2025. Accessed March 27, 2026.

Press D, Buss SS. Amyloid-targeted therapies for the treatment of Alzheimer's disease. In: UpToDate, DeKosky ST, Wilterdink JL (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through February 2026. Topic last updated October 31, 2025. Accessed March 30, 2026.