BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

LIBERVANT™ (diazepam) buccal film
NAYZILAM® (midazolam) nasal spray
VALTOCO® (diazepam) nasal spray
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 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.

Criteria:

- **Criteria for initial therapy:** Libervant (diazepam) buccal film, Nayzilam (midazolam) nasal spray or Valtoco (diazepam) nasal spray and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Neurologist

  2. Individual's age is **ONE** of the following:
     a. For **Libervant**: 2 to 5 years of age
     b. For **Valtoco**: 2 years of age or older
     c. For **Nayzilam**: 12 years of age or older

ORIGINAL EFFECTIVE DATE: 11/21/2019 | ARCHIVE DATE: | LAST REVIEW DATE: 05/15/2025 | LAST CRITERIA REVISION DATE: 05/15/2025

3. Individual has a confirmed diagnosis of **epilepsy** in an individual who has acute intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from the patient's usual seizure pattern

4. Stereotypic episodes of frequent seizure activity occur as **ONE** of the following:
    a. For **Libervant**: no more than one episode every 5 days and no more than 5 episodes per month
    b. For **Valtoco**: no more than one episode every 5 days and no more than 5 episodes per month
    c. For **Nayzilam**: no more than one episode every 3 days and no more than 5 episodes per month

5. Individual is on a stable antiepileptic regimen

6. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

7. Individual must **NOT** be actively using **illicit substances** **OR** have a history of risky, harmful, non-medical or inappropriate use of these and other substances that might be unhealthy, hazardous or a problem (i.e., multiple providers, multiple pharmacies, or multiple controlled substances)

8. Individual does **NOT** have the FDA-label contraindications of acute narrow-angle glaucoma

9. For **Nayzilam (midazolam) nasal spray**: Individual is not concurrently using moderate or strong CYP3A4 inhibitors (e.g., erythromycin, fluconazole, diltiazem, verapamil, amiodarone ketoconazole, itraconazole, posaconazole, others)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Libervant (diazepam) buccal film, Nayzilam (midazolam) nasal spray or Valtoco (diazepam) nasal spray and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Neurologist

2. Individual's condition has responded while on therapy with response defined as **TWO** of the following:
    a. No evidence of disease progression
    b. Reduction in number of recurrence stereotypic seizure activity
    c. Prolonged time to next stereotypic seizure activity

3. Individual has been adherent with the medication

4. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use as follows:
    a. Contraindications as listed in the criteria for initial therapy section
    b. Significant adverse effect such as:
        i. Profound sedation
        ii. Profound respiratory depression
        iii. Profound cognitive dysfunction
        iv. Coma
        v. Increased or emergent signs and symptoms of suicidal ideation and/or behaviors, worsening of depression, and/or any unusual changes in mood or behavior

6. Stereotypic episodes of frequent seizure activity occur as **ONE** of the following:
    a. For **Libervant**: no more than one episode every 5 days and no more than 5 episodes per month
    b. For **Valtoco**: no more than one episode every 5 days and no more than 5 episodes per month
    c. For **Nayzilam**: no more than one episode every 3 days and no more than 5 episodes per month

7. Individual must **NOT** be actively using **illicit substances** **OR** have a history of risky, harmful, non-medical or inappropriate use of these and other substances that might be unhealthy, hazardous or a problem (i.e., multiple providers, multiple pharmacies, or multiple controlled substances)

8. For **Nayzilam (midazolam) nasal spray**: Individual is not concurrently using moderate or strong CYP3A4 inhibitors (e.g., erythromycin, fluconazole, diltiazem, verapamil, amiodarone ketoconazole, itraconazole, posaconazole, others)

Renewal duration: 12 months

- 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:

Libervant (diazepam) buccal film is indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 2 to 5 years of age.

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Nayzilam (midazolam) nasal spray is indicated for acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 12 years of age.

Valtoco (diazepam) nasal spray is indicated for acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 2 years of age. The efficacy of Valtoco (diazepam) nasal spray is based on the relative bioavailability of Valtoco (diazepam) nasal spray compared to diazepam rectal gel in healthy adults. The effectiveness of diazepam rectal gel has been established in two adequate and well-controlled clinical studies in children and adults exhibiting seizure patterns.

The exact mechanism of action for midazolam and diazepam is not fully understood, but it is thought to involve potentiation of GABAergic neurotransmission resulting from binding at the benzodiazepine site of the GABA receptor. Midazolam and diazepam bind to stereospecific benzodiazepine receptors on the postsynaptic gamma aminobutyric acid (GABA) neuron at several sites within the central nervous system, including the limbic system, reticular formation. GABA is the chief inhibitory neurotransmitter in the developmentally mature mammalian central nervous system. Its principal role is to reduce neuronal excitability throughout the nervous system. Enhancement of the inhibitory effect of GABA on neuronal excitability occurs through increased neuronal membrane permeability to chloride ions. This shift in chloride ions results in hyperpolarization (a less excitable state) and stabilization. Benzodiazepine receptors and effects appear to be linked to the GABA-A receptors. Benzodiazepines do not bind to GABA-B receptors.

Diazepam rectal gel is a gel formulation of diazepam intended for rectal administration in the management of selected, refractory, patients with epilepsy, on stable regimens of AEDs, who require intermittent use of diazepam to control bouts of increased seizure activity. Evidence to support the use of diazepam rectal gel was adduced in two controlled trials. The trials enrolled patients with partial onset or generalized convulsive seizures who were suffering intermittent and periodic episodes of markedly increased seizure activity were characteristic and deemed to be of a kind for which a benzodiazepine would ordinarily be administered acutely. The clusters of seizure activity were not only stereotypic but were judged by those conducting and participating in these studies to be distinguishable from other seizures suffered by that patient.

Definitions:

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

Seizure Cluster:

- There is an established diagnosis of partial or generalized epilepsy that includes the following:
  - Documented history of seizure clusters lasting a minimum of 10 minutes
  - Seizure cluster pattern is composed of multiple (2 or more) partial or generalized seizures
  - Seizure cluster pattern is observable, stereotypical, and recognizably different from other non-cluster seizure activity
  - A second seizure in the seizure cluster occurs within 6 hours from the time of cluster onset
  - Seizure cluster pattern has been ongoing for at least 3 months

- Frequency of 3 or more seizure clusters per year

Resources:

Libervant (diazepam) buccal film product information, revised by Aquestive Therapeutics, Inc. 04-2024. Available at DailyMed http://fda.gov. Accessed February 18, 2025.

Nayzilam (midazolam) nasal spray product information, revised by UCB, Inc. 01-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 18, 2025.

Valtoco (diazepam) nasal spray product information, revised by Neurelis, Inc. 04-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed April 28, 2025.

Wilfong A. Seizures and epilepsy in children: Initial treatment and monitoring. In: UpToDate, Nordil DR, Dashe JF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through January 2025. Topic last updated December 02, 2024. Accessed February 25, 2025.

Wilfong A. Seizures and epilepsy in children: Refractory seizures. In: UpToDate, Nordil DR, Dashe JF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through January 2025. Topic last updated December 18, 2024. Accessed February 25, 2025.

ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). Identifier NCT01390220. Study to Evaluate the Safety and Efficacy of USL261 (Intranasal Midazolam) in patients with Seizure Clusters (ARTEMIS1). Last updated October 10, 2019. Available from: http://clinicaltrials.gov. Accessed February 23, 2022. Re-evaluated February 25, 2025.