BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES	
SECTION: DRUGS	
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NAYZILAM® (midazolam) nasal spray
VALTOCO® (diazepam) nasal spray

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

NAYZILAM® (midazolam) nasal spray
VALTOCO® (diazepam) nasal spray

Criteria:

- **Criteria for initial therapy:** Nayzilam (midazolam) nasal spray and Valtoco (diazepam) nasal spray are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

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

  2. Age of individual is **ONE** of the following:
     a. For **Nayzilam**: 12 years of age or older
     b. For **Valtoco**: 6 years of age or older

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

  4. Stereotypic episodes of frequent seizure activity occur as **ONE** of the following:
     a. For **Nayzilam**: no more than one episode every 3 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

  5. Individual is on a stable regimen of antiepileptic regimen

  6. There is no history of risky, harmful, or non-medical inappropriate use of these and other substances that might be unhealthy, hazardous, or a problem

  7. There are **NO** FDA-label contraindications, such as:
     a. Acute narrow-angle glaucoma

  Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Nayzilam (midazolam) nasal spray and Valtoco (diazepam) nasal spray is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  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 responded while on therapy
     a. Response is defined as **TWO** of the following:
        i. No evidence of disease progression
        ii. Reduction in number of recurrence stereotypic seizure activity
        iii. Prolonged time to next stereotypic seizure activity

3. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use
    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

4. Stereotypic episodes of frequent seizure activity occur as **ONE** of the following:
    a. For **Nayzilam**: no more than one episode every 3 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

5. There is no history of risky, harmful, or non-medical inappropriate use of these and other substances that might be unhealthy, hazardous, or a problem

6. There are no significant interacting drugs

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 a Non-Cancer Medications**

    2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

Description:

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 ≥ 6 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.

Resources:

Nayzilam (midazolam) nasal spray product information, revised by UCB, Inc. 02-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed on April 04, 2021.

Valtoco (diazepam) nasal spray product information, revised by Neurelis, Inc. 02-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed on April 04, 2021.

Wilfong A. Management of convulsive status epilepticus in children. In: UpToDate, Nordil DR, Dashe JF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed on April 04, 2021.

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. Accessed on April 04, 2021.

Drislane FW. Convulsive status epilepticus in adults: Treatment and prognosis. In: UpToDate, Garcia P, Edlow JA, Dashe JF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed on April 04, 2021.