Clinical Policy: Midazolam (Nayzilam)

Reference Number: ERX.NPA.123
Effective Date: 09.01.19
Last Review Date: 08.21
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Midazolam (Nayzilam®) is a benzodiazepine.

FDA Approved Indication(s)
Nayzilam 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 12 years of age and older.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Nayzilam is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Epilepsy with Seizure Cluster Episodes (must meet all)**:**

1. Diagnosis of partial or generalized epilepsy;
2. Prescribed by or in consultation with a neurologist;
3. Age ≥ 12 years;
4. Member is experiencing stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures);
5. Currently on a stable regimen of antiepileptic drugs (AEDs) (e.g., lamotrigine, gabapentin, topiramate, oxcarbazepine);
6. Dose does not exceed 2 doses per single episode (not to exceed 1 episode every 3 days or more than 5 episodes per month).

Approval duration: 6 months

B. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Epilepsy with Seizure Cluster Episodes (must meet all)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or documentation supports that member is currently receiving Nayzilam for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed 2 doses per single episode (not to exceed 1 episode every 3 days or 5 episodes per month).

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
AED: antiepileptic drug
FDA: Food and Drug Administration

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
phenytoin (Dilantin®)	**Generalized tonic-clonic and complex partial** • Initial dose is 100 mg (2 tablets) PO TID; may adjust dose every 7 to 10 days as necessary • Maintenance dosage: 300 to 400 mg/day	600 mg/day
carbamazepine (Tegretol®)	**Partial, generalized, and mixed types** • Age 12 years and older: Initial dose is 200 mg PO BID for the first week; may increase by adding up to 200 mg/day in 3 or 4 divided doses at weekly intervals to the minimum effective level (usually 800 to 1,200 mg/day)	Children age 12 to 15 years: 1,000 mg/day Children older than age 15 years: 1,200 mg/day Adults: 1,200 mg/day; rarely, up to 16,00 mg/day may be given
oxcarbazepine (Tegretol®)	**Partial seizure, monotherapy** • Age 12 to 16 years: Initial dosage 8 to 10 mg/kg orally once daily on an empty stomach, May increase in 8 to 10 mg/kg/day increments at weekly intervals to achieve a target dose over 2 to 3 weeks. ○ Target maintenance dose is based on weight; (20-29 kg, 900 mg/day) (29.1-39 kg, 1,200 mg/day); and (greater than 39 kg, 1,800 mg/day) • Age 17 to 18 years: Initial dosage is 600 mg/day PO QD for 1 week on an empty stomach. May increase in 600 mg/day increments at weekly intervals to 1,200 to 2,400 mg/day • Adult initial dosage: 600 mg/day in 2 divided doses. Increase every third day by 300 mg/day to achieve a dose of 1,200 mg/day **Partial seizure; adjunct**	**Monotherapy** Age 12 to 16 years: 600 mg/day Age 17 years and older: 2,400 mg/day **Adjunct** Age 12 to 16 years: 600 mg/day Age 17 years and older: 1,200 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	• Age 12 to 16 years: Initial dosage is 8 to 10 mg/kg/day PO in 2 divided doses ○ Maintenance dosage should be achieved over 2 weeks, and is dependent upon patient weight: (20 to 29 kg, 900 mg/day); (29.1 to 39 kg, 1,200 mg/day); and (greater than 39 kg, 1,800 mg/day) • Age 17 and older: initial dosage is 300 mg PO BID; may increase weekly by up to 600 mg/day	
phenobarbital	**Epilepsy** • Pediatrics: 15 to 50 mg PO BID or TID • Adults: 50 to 100 mg tablet PO BID or TID	
gabapentin (Neurontin®)	**Partial seizure; adjunct** • Age 12 years and older: Initial dose is 300 mg PO TID • Maintenance is 300 to 600 mg PO TID	Doses up to 2,400 mg/day have been well tolerated; doses of 3,600 mg/day have been administered to a small number of patients for a short duration
pregabalin (Lyrica®)	**Partial seizure** • Age 12 to 16 years; Adjunct: Weight below 30 kg initial dose is 3.5 mg/kg/day PO in 2 or 3 divided doses ○ Weight above 30 kg initial dose is 2.5 mg/kg/day PO in 2 or 3 divided doses • Age 17 and above; Adjunct: Initial dose is 150 mg/day PO in 2 or 3 divided doses;	Age 12-16 with weight below 30 kg: 14 mg/kg/day in 2 or 3 divided doses Age 12-16 with weight above 30 kg and ages 17 and older: 10 mg/kg/day or 600 mg/day in 2 or 3 divided doses
valproic acid (Depakote®)	**Complex partial epileptic seizure** • Monotherapy: Initial dose is 10 to 15 mg/kg/day PO (give in 2 to 3 divided doses if total daily dose exceeds 250 mg), may increase dosage 5 to 10 mg/kg/day at 1-week intervals to achieve optimal clinical response • Adjunct: May be added to the regimen at an initial dose of 10 to 15 mg/kg/day PO (give in 2 to 3 divided doses if total daily dose exceeds 250 mg); may increase dosage 5 to 10 mg/kg/day at 1-week intervals to achieve optimal clinical response	60 mg/kg/day or less with a therapeutic serum range of 50 to 100 mcg/mL
topiramate (Topamax®)	**Partial seizure** • Age 12 years and older; Monotherapy: Initial dosage is 25 mg PO BID (morning and evening) for the first week; second week, 50 mg PO BID; third week, 75 mg PO BID; fourth week, 100 mg PO BID; fifth week, 150 mg PO BID; sixth week, 200 mg PO BID. • Age 12 to 16 years; Adjunct: Initial dosage is 25 mg or less (1 to 3 mg/kg/day) PO at bedtime for the first week, then increase dosage by 1 to 3 mg/kg/day (in 2 divided	400 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	doses) at 1 to 2 week intervals to the usual effective dosage of 5 to 9 mg/kg/day. • Age 17 years and older; Adjunct: Initial dosage is 25 to 50 mg/day PO; may increase dosage by 25 to 50 mg/day at 1-week intervals to the usual maintenance dose of 200 to 400 mg/day in 2 divided doses; titrating in increments of 25 mg/day every week may delay the time to reach an effective dose; doses above 400 mg/day have not been shown to improve responses **Tonic-clonic seizure, primary generalized** • Age 12 years and up; Monotherapy: First week initial dosage is 25 mg PO BID; second week, 50 mg PO BID; third week, 75 mg PO BID; fourth week, 100 mg PO BID; fifth week, 150 mg PO BID; sixth week 200 mg PO BID (usual maintenance dose) • Age 12 to 16 years; Adjunct: Initial dosage is 25 mg or less (1 to 3 mg/kg/day) PO at bedtime for the first week, then increase dosage by 1 to 3 mg/kg/day (in 2 divided doses) at 1 to 2 week intervals to the usual effective dosage of 5 to 9 mg/kg/day in 2 divided doses • Age 17 years and older; Adjunct: Initial dosage is 25 to 50 mg/day PO; may increase dosage by 25 to 50 mg/day at 1-week intervals to the usual maintenance dose of 400 mg/day in 2 divided doses; titrating in increments of 25 mg/day every week may delay the time to reach an effective dose	
levetiracetam (Keppra®)	**Partial seizure & tonic-clonic seizure, primary generalized** • Age 4 to 16 years; Adjunct: ○ Weight 20 to 40 kg: Initial dose is 250 mg PO BID; titration, increase by increments of 500 mg/day in 2 divided doses every 2 weeks ○ Weight greater than 40 kg: Initial dose is 500 mg PO BID; titration, increase by increments of 1,000 mg/day every 2 weeks in 2 divided doses • Age 16 years and older; Adjunct: Initial dose is 500 mg PO BID; titration, may increase by increments of 1,000 mg/day every 2 weeks in 2 divided doses	Age 4 to 16 years with weight 20 to 40 kg: 1,500 mg/day Age 4 to 16 years with weight above 40 kg, as well as age 16 years and older: 3,000 mg/day

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): narrow-angle glaucoma
- Boxed warning(s): concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death; use of benzodiazepines exposes users to

risks of abuse, misuse, and addiction, which can lead to overdose or death; continued use of benzodiazepines may lead to clinically significant physical dependence

Appendix D: General Information

- Seizure clusters can be defined as multiple seizures that occur within a short period of time. These seizures will happen in an increased frequency from the patient's normal seizure activity. Thus, they are distinguishable from a person's typical seizure pattern. The definition for a specific time period varies. Various studies use the following time frames: two to four seizures per < 48 hours; 3 seizures per 24 hours; or two generalized tonic-clonic or three complex partial seizures in 4 hours. Seizure clusters are also known as acute-repetitive seizures, serial seizures, crescendo seizures, and seizure flurries, which highlight the repetitive nature of the seizures. Seizure clusters are a form of seizure emergency that have potential to evolve into prolonged seizures and status epilepticus.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Seizure clusters in patients with epilepsy	1 spray (5 mg) into 1 nostril. If no response 10 minutes after the initial dose: a second dose of 1 spray (5 mg) into the opposite nostril may be given	2 doses/single episode; do not treat more than 1 episode every 3 days or more than 5 episodes/month

VI. Product Availability

Single-dose nasal spray unit: 5 mg/0.1 mL

VII. References

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Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	06.25.19	08.19
3Q 2020 annual review: no significant changes; references reviewed and updated.	05.04.20	08.20
3Q 2021 annual review: no significant changes; references reviewed and updated.	04.20.21	08.21

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of

physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.