Clinical Policy Title:	midazolam
Policy Number:	RxA.417
Drug(s) Applied:	Nayzilam®
Original Policy Date:	03/06/2020
Last Review Date:	09/14/2021
Line of Business Policy Applies to:	All lines of business

Background

Midazolam (Nayzilam® ®) is a benzodiazepine. It 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.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
midazolam (Nayzilam®)	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.

Dosage Forms

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

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

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 5 episodes per month).

Approval Duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

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

1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
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
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
AED: Antiepileptic Drug
FDA: Food and Drug Administration

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
phenytoin (Dilantin®)	<u>Generalized tonic-clonic and complex partial</u> • Initial dose is 100 mg (2 tablets) orally three times daily; may adjust dose every 7 to 10 days as necessary. • Maintenance dosage: 300 to 400 mg/day.	600 mg/day
carbamazepine (Tegretol®)	<u>Partial, generalized, and mixed types</u> Age 12 years and older: Initial dose is 200 mg orally twice daily 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 1,600 mg/day may be given.
oxcarbazepine (Trileptal®, Oxtellar XR®)	<u>Partial seizure, monotherapy</u> • Age 12-16 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	<u>Monotherapy</u> Age 12 to 16 years: 600 mg/day Age 17 years and older: 2,400 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	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 orally once daily 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 <u>Partial seizure; adjunct</u> • Age 12 to 16 years: Initial dosage is 8 to 10 mg/kg/day orally in 2 divided doses o 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, 1200 mg/day); and (greater than 39 kg, 1,800 mg/day) • Age 17 and older: initial dosage is 300 mg orally twice daily; may increase weekly by up to 600 mg/day.	<u>Adjunct</u> Age 12 to 16 years: 600 mg/day Age 17 years and older: 1,200 mg/day
phenobarbital	<u>Epilepsy</u> • Pediatrics: 15 to 50 mg orally twice daily or three times daily • Adults: 50 to 100 mg tablet orally twice daily or three times daily.	
gabapentin (Neurontin®)	<u>Partial seizure; adjunct</u> • Age 12 years and older: Initial dose is 300 mg orally three times daily Maintenance is 300 to 600 mg orally three times daily.	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®)	<u>Partial seizure</u> • Age 12-16; Adjunct: o Weight below 30 kg initial dose is 3.5 mg/kg/day orally in 2 or 3 divided doses o Weight above 30 kg initial dose is 2.5 mg/kg/day orally in 2 or 3 divided doses • Age 17 years and older; Adjunct: Initial dose is 150 mg/day orally in 2 or 3 divided doses.	Age 12 to 16 years with weight below 30 kg: 14 mg/kg/day in 2 or 3 divided doses. Age 12 to 16 years with weight above 30 kg and ages 17 and older: 10 mg/kg/day or 600 mg/day in 2 or 3 divided doses.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
valproic acid (Depakote®)	Complex partial epileptic seizure • Monotherapy: Initial dose is 10 to 15 mg/kg/day orally (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 orally (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 orally twice daily (morning and evening) for the first week; second week, 50 mg orally twice daily; third week, 75 mg orally twice daily; fourth week, 100 mg orally twice daily; fifth week, 150 mg orally twice daily; sixth week, 200 mg orally twice daily • Age 12 to 16 years; Adjunct: Initial dosage is 25 mg or less (1 to 3 mg/kg/day) orally 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. • Age 17 years and older; Adjunct: Initial dosage is 25 to 50 mg/day orally; 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 older; Monotherapy: First week initial dosage is 25 mg orally twice daily; second week, 50 mg orally twice daily; third week, 75 mg orally twice daily; fourth week, 100 mg orally twice daily; fifth week, 150 mg orally twice daily; sixth week 200 mg orally twice daily (usual maintenance dose) • Age 12 to 16 years; Adjunct: Initial dosage is	400 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	25 mg or less (1 to 3 mg/kg/day) orally 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 orally; 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 orally twice daily; 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 orally twice daily; 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 orally twice daily; 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.

Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Narrow-angle glaucoma;
  - Hypersensitivity.

- Boxed Warning(s):
  - Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death.
  - The use of benzodiazepines, including Nayzilam® , exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Before prescribing Nayzilam® and throughout treatment, assess each patient's risk for abuse, misuse, and addiction.
  - Although Nayzilam® is indicated only for intermittent use, if used more frequently than recommended, abrupt discontinuation or rapid dosage reduction of Nayzilam® may precipitate acute withdrawal

reactions, which can be life-threatening. For patients using Nayzilam® more frequently than recommended, to reduce the risk of withdrawal reactions, use a gradual taper to discontinue Nayzilam®.

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.

References

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Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established	01/2020	03/06/2020
Policy was reviewed: 1. Clinical Policy Title was updated. 2. Line of Business Policy Applies to was updated to all lines of business. 3. Initial and Continued approval duration was updated to include Medicaid & Commercial approval duration. 4. Continued therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance…". 5. Updated appendix C: added "hypersensitivity" in contraindication(s). 6. References were reviewed and updated.	7/22/2020	9/14/2020
Policy was reviewed:	06/03/2021	9/14/2021

1. Statement about provider sample ‘‘The provision of provider samples does not guarantee coverage…” was added to Clinical Policy. 2. Continued Therapy Criteria II.A.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance...". 3. Therapeutic Alternatives verbiage was rephrased to "Below are suggested therapeutic alternatives based on clinical guidance..". 4. Statement about drug listing format in Appendix B is rephrased to "Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only". 5. Appendix C boxed warning was updated to include “The use of benzodiazepines, including Nayzilam® , exposes users…” 6. References were reviewed and updated.		