Clinical Policy: Diazepam Nasal Spray (Valtoco)

Reference Number: IN.CP.PMN.216
Effective Date: 12.01.19
Last Review Date: 10.20
Line of Business: Commercial, HIM, Medicaid

Revision Log

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

Description

Diazepam nasal spray (Valtoco®) is a benzodiazepine.

FDA Approved Indication(s)

Valtoco 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 6 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.

It is the policy of health plans affiliated with Centene Corporation® that Valtoco 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. Age ≥ 6 years;
3. Member is experiencing stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures);
4. Currently on a stable regimen of antiepileptic drugs (AEDs) (e.g., lamotrigine, gabapentin, topiramate, oxcarbazepine);
5. Dose does not exceed 2 doses per single episode (not to exceed 1 episode every 5 days or 5 episodes per month) (*refer to section V for age and weight specific dosing*).

Approval duration: 6 months

B. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

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

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Valtoco 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 5 days or 5 episodes per month) (*refer to section V for age and weight specific dosing*).

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 policies – CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid 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	Children age 12 to 15 years: 1,000 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	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 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 (Tegretol®)	**Partial seizure, monotherapy**
	• Age 12-16 years: Initial dosage 8 to 10 mg/kg PO QD 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
	• 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, 1200 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
		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

phenobarbital	**Epilepsy** • Pediatrics: 15 to 50 mg PO BID or TID • Adults: 50 to 100 mg tablet PO BID or TID	

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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 12-16; 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 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
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	400 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	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 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 older; 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	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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	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	well as age 16 years and older: 3,000 mg/day

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

Appendix C: Contraindications/Boxed Warnings

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

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

<table>
<tr><th>Indication</th><th>Dosing Regimen</th><th>Maximum Dose</th></tr>
<tr><td>Seizure clusters in patients with epilepsy</td><td>Spray initial dose* into nostril. If no response 4 hours after the initial dose, a second dose may be given.

*The recommended dose of Valtoco nasal spray is 0.2 mg/kg or 0.3 mg/kg, depending on the patient's age and weight. The following table provides the acceptable weight ranges for each dose and age category, such that patients will receive between 90% and 180% of the calculated recommended dose.
<table>
<tr><th colspan="3">Dose</th><th colspan="2">Administration</th></tr>
<tr><th>6-11 years (0.3 mg/kg)
Weight (kg)</th><th>≥ 12 years (0.2 mg/kg)
Weight (kg)</th><th>Dose (mg)</th><th># of Nasal Spray Devices</th><th># of Sprays</th></tr>
<tr><td>10-18</td><td>14-27</td><td>5</td><td>One 5 mg device</td><td>1 spray in one nostril</td></tr>
<tr><td>19-37</td><td>28-50</td><td>10</td><td>One 10 mg device</td><td>1 spray in one nostril</td></tr>
<tr><td>38-55</td><td>51-75</td><td>15</td><td>Two 7.5 mg devices</td><td>1 spray in each nostril</td></tr>
<tr><td>56-74</td><td>≥ 76</td><td>20</td><td>Two 10 mg devices</td><td>1 spray in each nostril</td></tr>
</table>
</td><td>2 doses/single episode; do not treat more than 1 episode every 5 days or more than 5 episodes/month</td></tr>
</table>

VI. Product Availability

Nasal spray: 5 mg/0.1 mL, 7.5 mg/0.1 mL, 10 mg/0.1 mL

VII. References

1. Valtoco Prescribing Information. San Diego, CA: Neurelis, Inc.; January 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211635s000lbl.pdf. Accessed January 13, 2020.
2. Grand mal seizure. (2018, December 07). Retrieved June 4, 2019, from https://www.mayoclinic.org/ diseases-conditions/grand-mal-seizure/symptoms-causes/syc-20363458. Accessed October 3, 2019.
3. Kumar A. Complex partial seizure. Available at: https://www.ncbi.nlm.nih.gov/books/NBK519030/. Accessed October 3, 2019.
4. Schachter SC. Seizure clusters. Available at: https://www.epilepsy.com/learn/professionals/refractory-seizures/potentially-remediable-causes/seizure-clusters. Accessed October 3, 2019.
5. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed October 3, 2019.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	10.22.19	11.19
Policy updated per new FDA approved labeling.	01.13.20	
Removed Specialist and T/F of Diastate. Transitioned to local policy	08.24.20	
Annual Review – No changes	10/14/2020	10/14/2020

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.