Drug Monograph

Drug Name: **Valtoco® (diazepam) Nasal Spray**
Drug Class: **Anticonvulsant**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Valtoco nasal spray is available in 5 mg, 7.5 mg and 10 mg strengths. This product is supplied and packaged in doses of 5 mg, 10 mg, 15 mg or 20 mg.
Manufacturer:	Manufactured for: Neurelis, Inc., San Diego, CA 92130.
Summary of Findings:	In a randomized, double-blind study of diazepam rectal gel based on the relative bioavailability of the nasal spray compared to diazepam rectal gel (N=91) Valtoco showed a statistically significant improvement in seizure frequency for the treatment group (zero seizures) compared to placebo (0.3 seizures) per hour ($p < 0.0001$). The most common adverse reactions during the study were somnolence, headache, diarrhea, ataxia, dizziness, euphoria, incoordination, and rash. Patients should be monitored for risk of concomitant use with opioids, CNS depression, suicidal behavior and ideation, and glaucoma while using this medication.

Status Recommendation:	☐ Clinical Edit	☒ PA Required
	☐ Open Access	☐ PDL
Type of PA Criteria:	☒ Appropriate Indications	☐ Non-Preferred
	☐ No PA Required	☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

Epilepsy is a brain disorder characterized by a predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological and social consequences of this condition. Diagnosis of epileptic seizures is made through physical examination, laboratory tests (such as prolactin levels, serum levels of anticonvulsants and cerebrospinal fluid), and imaging studies (such as MRI, CT, EEG). Typically the diagnosis requires the occurrence of at least 2 unprovoked seizures. Treatment goals in patients with epileptic seizures are to achieve seizure-free status without adverse effects. There are multiple treatment options for anticonvulsant medications including sodium channel blockers (phenytoin, carbamazepine, lamotrigine), GABA-A receptor enhancers (phenobarbital, benzodiazepines), NMDA receptor blockers (felbamate), AMPA receptor blockers (topiramate), H0current modulates (gabapentin) just to name a few. Monotherapy is the preferred route of therapy to decrease the risk of adverse effects however many patients require multiple treatment options to achieve seizure-free status. It is important to note that the type of seizure (absence, tonic or atonic, myoclonic and tonic-clonic) often dictates which anticonvulsant is used. In addition to medication management, non-pharmacological interventions such as diet and surgical interventions such as vagal nerve stimulation and lobectomy are also used for treatment. For this review, we will be looking at the acute treatment of intermittent, stereotypic episodes of frequent seizure activity.

Dosage Form [1]

Valtoco nasal spray is available in 5 mg, 7.5 mg and 10 mg strengths. This product is supplied and packaged in doses of 5 mg, 10 mg, 15 mg or 20 mg.

Manufacturer [1]

Manufactured for: Neurelis, Inc., San Diego, CA 92130

Indication(s) [1]

Valtoco is indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity that are distinct from a patient's usual seizure pattern in patients with epilepsy 6 years of age and older.

Clinical Efficacy [1,2] (mechanism of action/pharmacology, comparative efficacy)

Valtoco is a diazepam nasal spray thought to bind to stereospecific benzodiazepine receptors on the postsynaptic GABA-A neuron at several sites within the central nervous system. This inhibitory effect of GABA results increased neuronal membrane permeability to chloride ions and ultimately a less excitable state.

Pharmacokinetics:

Absorption	Peak absorption in 1.5 hours. Steady-state volume of distribution 0.8 to 1.0 L/Kg
Metabolism	CYP2C19 and CYP3A4 isozyme oxidative hepatic metabolism
Distribution	Extensive plasma protein binding
Half-life	49.2 hours (10 mg dose)

Clinical Trials Experience

STUDY 1 DESIGN	The effectiveness of Valtoco has been established in a randomized, double-blind study of diazepam rectal gel based on the relative bioavailability of the nasal spray compared to diazepam rectal gel (N=91).
INCLUSION CRITERIA	• Adults and children exhibiting seizure patterns.
EXCLUSION CRITERIA	• Patients that did not meet inclusion criteria.
TREATMENT REGIMEN	Patients were given an initial dose at the onset of an identified seizure episode. Children received a second dose in 4 hours and were observed for a total of 12 hours. Adults were given a second dose at 4 hours and again at 12 hours and were observed for a total of 24 hours. The primary outcome of the study was seizure frequency during the period of observation and a global assessment that took into account the severity and nature of the seizures as well as their frequency.
RESULTS	Diazepam had a statistically significant improvement in seizure frequency for the treatment group (zero seizures) compared to placebo (0.3 seizures) per hour ($p < 0.0001$). All three categories of the global assessment were also found to be statistically significant for diazepam rectal gel over placebo ($p < 0.0001$).
SAFETY	Discussed in the Adverse Effects section below.

Contraindications (1)

- Valtoco is contraindicated in patients with:
  - Known hypersensitivity to diazepam
  - Acute narrow angle glaucoma

Warnings and Precautions (1.2)

- **Risk of Concomitant Use with Opioids:** Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. If use is warranted, the lowest effective dosages and minimum durations should be used and patients monitored for signs and symptoms of respiratory depression and sedation.
- **CNS Depression:** Benzodiazepines may produce CNS depression and patients should be use caution when engaging in hazardous activities requiring mental alertness.
- **Suicidal Behavior and Ideation:** Antiepileptic drugs can increase the risk of suicidal thoughts or behavior so patients should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

- **Glaucoma:** Benzodiazepines can cause increased intraocular pressure in patients with glaucoma and should be avoided in patients with narrow-angle glaucoma.
- **Risk of Serious Adverse Reactions in Infants due to Benzyl Alcohol Preservative:** Valtoco is not approved for use in neonates or infants due to a potential of serous and fatal adverse reactions including "gasping syndrome" can with these patients.

Adverse Effects [1]

Most common, ≥ 1 %	Diazepam Rectal Gel (n = 101) %	Placebo (n = 104) %
Somnolence	23	8
Headache	5	4
Diarrhea	4	<1
Ataxia	3	<1
Dizziness	3	2
Euphoria	3	0
Incoordination	3	0
Rash	3	0
Asthma	2	0
Vasodilation	2	0

Drug Interactions [1]

- **Effect of Concomitant Use of Benzodiazepines and Opioids:** The use of benzodiazepines and opioids increases the risk of respiratory depression with the potential to significantly worsen opioid-related respiratory depression. Dosages and duration should be limited of concomitant use of benzodiazepines and opioids and patients should be followed closely for respiratory depression and sedation.
- **CNS Depressants and Alcohol:** Concomitant use of other CNS depressants or alcohol may increase CNS-depressant effects of diazepam.
- **Effects of Other Drugs on Valtoco Metabolism:** Medications that inhibit/induce CYP2C19 and CYP3A4 activity can have potential interactions with diazepam.
- **Effect of Valtoco on the metabolism of Other Drugs:** Diazepam can have potential interactions in metabolism of drugs that are substrates of CYP2C19 and CYP3A4 and can lead to a potential drug-drug interaction.

Dosage and Administration [1]

The recommended dose of Valtoco nasal spray is 0.2 mg/kg or 0.3 mg/kg depending of patient's age and weight. A second dose, when needed, should be administered at least 4 hours after the initial dose. A maximum of 2 doses should be used for a single episode with a recommendation of treating no more than once episode every five days and no more than five episodes per month. It is important to note that Valtoco is for intranasal use only and should not be primed or used for more than one administration per device. The following chart shows the complete dosage recommendations:

Dose Based on Age and Weight			Administration	
6 to 11 Years of Age (0.3 mg/kg)	12 Years of Age and Older (0.2 mg/kg)	Dosage (mg)	Number of Nasal Spray Devices	Number of Sprays
Weight (kg)	Weight (kg)			
10 to 18	14 to 27	5	One 5 mg device	One spray in one nostril
19 to 37	28 to 50	10	One 10 mg device	One spray in one nostril
38 to 55	51 to 75	15	Two 7.5 mg devices	One spray in one nostril
56 to 74	76 and up	20	Two 10 mg devices	One spray in one nostril

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**
Diazepam	Valtoco	Neurelis	0.2 or 0.3 mg/kg	$560/2 pack
Diazepam	Diastat (generic available)	Bausch Health	2.5, 10, or 20 mg rectal injection	$350/pack

** Wholesale Acquisition Cost

Conclusion

Valtoco is a diazepam nasal spray thought to bind to stereospecific benzodiazepine receptors on the postsynaptic GABA-A neuron at several sites within the central nervous system. In a randomized, double-blind study of diazepam rectal gel based on the relative bioavailability of the nasal spray compared to diazepam rectal gel (N=91) Valtoco showed a statistically significant improvement in seizure frequency for the treatment group (zero seizures) compared to placebo (0.3 seizures) per hour ($p < 0.0001$). The most common adverse reactions during the study were somnolence, headache, diarrhea, ataxia, dizziness, euphoria, incoordination, and rash.

Recommendation

The MO HealthNet Division recommends prior authorization status for this product.

References

1) Product Information: Valtoco (diazepam nasal spray), Neurelis, Inc., San Diego, CA 92130, 2020.
2) Ko, David MD, Benbadis, Selim MD, et al. Epilepsy and Seizures February 13, 2020 Medscape.

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Date: March 29, 2020