Drug Monograph

Drug Name: **Nayzilam® (midazolam) Nasal Spray**
Drug Class: **Anticonvulsant, Benzodiazepine**
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 Form:	Nayzilam is available as an intranasal spray containing 5 mg/0.1 ml of midazolam.
Manufacturer:	Manufactured For: UCB, Inc., Smyrna, GA 30080.
Summary of Findings:	The efficacy of Nayzilam was demonstrated in one randomized, double-blind, placebo-controlled trial in 292 patients with epilepsy. The primary measure of efficacy was number of patients who met the criteria for treatment success after administration of the double-blind dose in the comparative phase (CP). Treatment success is defined as achieving both of the following: 1) termination of seizure within 10 minutes after drug administration, and 2) no recurrence of seizure beginning 10 minutes after to 6 hours after drug administration. There was a statistically significant difference in the number of patients who met the criteria for treatment success of intranasal midazolam than placebo-treated patients (53.7% vs 34.4%; p = 0.0109).
Status Recommendation:	☒ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☐ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Non-Preferred Agent ☒ Appropriate Indications ☐ No PA Required

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]

Epilepsy is a chronic neurological condition in which there is a disruption in the electrical communication between neurons. Acute repetitive seizures, or cluster seizures, are known as repetitive or serial seizures with return to baseline between events. 3.4 million people in the United States have epilepsy. Prevalence of seizure clustering can range from very low up to 60% of epilepsy cases. Seizure clusters are not as life threatening as status epilepticus, but still have significant impact on patient health. Seizure clusters can result in emergency room visits, missed school and work, and a greater utilization of health care resources.

Dosage Form [2]

Nayzilam is available as a single-dose nasal spray unit containing 5 mg of midazolam per 0.1 ml solution.

Manufacturer [2]

Manufactured For: UCB, Inc., Smyrna, GA 30080.

Indication(s) [2]

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.

Clinical Efficacy [2,3,4] (mechanism of action/pharmacology, comparative efficacy)

Nayzilam is thought to involve potentiation of GABAergic neurotransmission resulting from binding at the benzodiazepine site of the $GABA_A$ receptor.

Pharmacokinetics:

Absorption	Time to peak: 10 minutes
Metabolism	Metabolized extensively by hepatic CYP3A4, 60% to 70% to active metabolite, 1-hydrozy midazolam, and 2 minor metabolites: 4-hydroxy metabolite and 1,4-dihydroxy metabolite.
Excretion	Urine: Primarily as glucuronide conjugates of hydroxylated metabolites Feces: n/a
Half-life	2.1 - 6.2 hours

Clinical Trials Experience

STUDY 1 DESIGN (ARTEMIS1)	Phase III, randomized, double-blind, placebo-controlled study (n = 292)

INCLUSION CRITERIA	• Has a competent, adult caregiver who can recognize and observe seizure cluster episodes
	• Has an established diagnosis of partial or generalized epilepsy that includes the following:
	  ○ A documented history of seizure clusters lasting a minimum of 10 minutes
	  ○ Seizure cluster pattern is observable, stereotyped, and recognizably different from the subject's other non-cluster seizure activity (if any)
	  ○ A second seizure in the seizure cluster typically occurring within 6 hours from the time of cluster recognition
	  ○ A seizure cluster pattern composed of multiple (≥ 2) partial or generalized seizures
	  ○ A seizure cluster pattern established > 3 months before Visit 1
	  ○ A frequency of ≥ 3 seizure clusters during the year before Visit 1
	  ○ At least 1 seizure cluster occurring ≤ 4 months before Visit 1
	  ○ Seizure cluster pattern is confirmed by a central reviewer
	• Currently on a stable regimen of anti-epileptic drugs (AEDs) with no changes in type of AEDs since Visit 1 and for ≥ 7 days before Visit 2, with or without intermittent use of benzodiazepines at a constant dose
	• Weight is 40 kg to 125 kg, inclusive

EXCLUSION CRITERIA	• Has a neurological disorder that is likely to progress in the next year • Has severe chronic cardio-respiratory disease • Has had psychogenic, non-epileptic seizure(s) within the 5 years before Visit 1 • Has a history of their stereotypical seizure cluster progressing to status epilepticus within the 2 years before Visit 1 • Has a history of acute narrow-angle glaucoma. • Has had active suicidal plan/intent or active suicidal thoughts in the 6 months before Visit 1 or a suicide attempt in the past 5 years

	• Currently using a vagal nerve stimulator (VNS) unless the device has been implanted for at least 6 months and the setting stable for 4 weeks before Visit 1
TREATMENT REGIMEN	Patients were randomized (2:1) to receive intranasal Nayzilam 5 mg (n=134) or placebo (n=67).
RESULTS	The primary measure of efficacy was number of patients who met the criteria for treatment success after administration of the double-blind dose in the comparative phase (CP). Treatment success is defined as achieving both of the following: 1) termination of seizure within 10 minutes after drug administration, and 2) no recurrence of seizure beginning 10 minutes after drug administration to 6 hours after. A significantly greater proportion of intranasal Nayzilam than placebo-treated patients achieved treatment success (53.7% vs 34.4%; p = 0.0109).
SAFETY	Discussed in the Adverse Effects section below.

Contraindications [2]

- Known hypersensitivity to midazolam
- Acute narrow-angle glaucoma

Warnings and Precautions [2,3]

- CNS depression from concomitant use with other CNS depressants or moderate or strong CYP3A4 inhibitors: May cause an increased CNS-depressant effect when used with alcohol or other CNS depressants. Concomitant use with moderate or strong CYP3A4 inhibitors may result in prolonged sedation because of a decrease in plasma clearance of midazolam.
- Suicidal behavior and ideation: Antiepileptic drugs increase the risk of suicidal ideation and behavior.
- Impaired cognitive function: Midazolam is associated with a high incidence of partial or complete impairment of recall for the next several hours.
- Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death.
- Serious cardiorespiratory adverse reactions including respiratory depression, airway obstruction, oxygen desaturation, apnea, respiratory arrest and sometimes death or prolonged neurologic injury.

Adverse Effects [2,3]

Most common, ≥ 2%	Nayzilam (n = 175) %
Somnolence	10
Nasal Discomfort	9
Headache	4
Throat Irritation	3
Rhinorrhea	3
Dysarthria	2
Product Taste Abnormal	2
Lacrimation Increased	2

Drug Interactions [2,3]

- CYP3A4 Inhibitors: Prolonged sedation due to a decrease in plasma clearance of midazolam. Avoid co-administration with moderate to strong inhibitors such as erythromycin, diltiazem, verapamil, ketoconazole, itraconazole, clarithromycin.
- Opioids: Concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Medications include: morphine, hydrocodone, oxymorphone, codeine, fentanyl.
- CNS Depressants: Concomitant use of barbiturates, alcohol, anxiolytics, tranquilizers, muscle relaxants, antipsychotics, and opioids may increase the risk of hypoventilation, airway obstruction, desaturation or apnea and may contribute to profound or prolonged drug effect.

Dosage and Administration [2,3]

- Administer one spray (5 mg) intranasally into one nostril once. A second dose into the opposite nostril may be administered after 10 minutes if the patient has not responded to the initial dose.
- Recommended that Nayzilam be used to treat no more than one episode every three days and no more than 5 episodes per month.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**
Midazolam	Nayzilam	UCB, Inc.	5 mg once; up to 10 mg per 3 days	$275 per device

** Wholesale Acquisition Cost

Conclusion

Nayzilam is indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (seizure clusters) that are distinct from a patient's usually seizure pattern in patients with epilepsy 12 years of age and older. The efficacy of Nayzilam was demonstrated in one randomized, double-blind, placebo-controlled trial in 292 patients. There was a statistically

significant difference in the number of patients who met the criteria for treatment success (termination of seizure within 10 minutes after drug administration, and no recurrence of seizure beginning 10 minutes to 6 hours after drug administration). The most common adverse reactions in patients taking Nayzilam (>2%) were somnolence, headache, nasal discomfort, throat irritation and rhinorrhea.

Recommendation

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

References

1) Epilepsy Foundation. https://www.epilepsy.com/learn/types-seizures. Accessed October 23, 2019.
2) Product Information: Nayzilam® (midazolam), 2019. Proximagen, LLC, Plymouth, MN 55441.
3) Nayzilam: Product Information. Lexicomp [database online]. Indianapolis, IN: Wolters Kluwer Health, Inc. http:online.lexi.com. Accessed October 23, 2019.
4) Safety and efficacy of midazolam nasal spray in the outpatient treatment of patients with seizure clusters- a randomized, double-blind, placebo-controlled trial. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/results/NCT01390220.

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