Clinical Policy: Agents for Epilepsy and Seizures

Reference Number: MDN.CP.PMN.352
Effective Date: 01.01.25
Last Review Date: 10.3.24
Line of Business: Meridian Illinois Medicaid Revision Log

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

Description

The following are agents for seizures and/or epilepsy requiring prior authorization: Stiripentol (Diacomit), Cannabidiol (Epidiolex), Vigabatrin (Sabril), Clobazam (Onfi, Sympazan), Midazolam (Nayzilam), Rufinamide (Banzel), Pregabalin (Lyrica [brand]), Lyrica CR), Diazepam Nasal Spray (Valtoco), Lacosamide (Motpoly XR, Vimpat).

Policy/Criteria

It is the policy of health plans affiliated with Centene Corporation® that the above agents for seizures/epilepsy are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Epilepsy or Seizures (must meet all)**:**

1. Diagnosis of epilepsy or seizure disorder;
2. Dose does not exceed FDA dosing (See section V)

Approval duration: 12 months (Quantity Limits: may override if medically necessary/standard of care, acute treatment where a second dose is needed for another location, i.e. school).

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

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Epilepsy or Seizures (must meet all)**:**

1. If request is for a dose increase, new dose does not exceed dose listed in section V) (*refer to section V for age and weight specific dosing*).

Approval duration: 12 months

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

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: 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.PMN.53 for Medicaid or evidence of coverage documents.

III~~V~~. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AED: antiepileptic drug
FDA: Food and Drug Administration
LGS: Lennox-Gastaut syndrome

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
diazepam rectal gel (Diastat®)	Age-based dosing, administered rectally: 2-5 years: 0.5 mg/kg/dose 6-11 years: 0.3 mg/kg/dose 12 years and older: 0.2 mg/kg/dose A second dose, when required, may be given 4-12 hours after the first dose.	0.5 mg/kg/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 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	**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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	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	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	
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

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 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	**Partial seizure**	400 mg/day

(Topamax®)	• 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 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	

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	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

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

Valtoco

- Contraindication(s): acute narrow-angle glaucoma, known hypersensitivity to diazepam

- Boxed warning(s): concomitant use with opioids; abuse, misuse, and addiction; dependence and withdrawal reactions

Epidiolox

- Contraindication(s): hypersensitivity to cannabidiol or any of the ingredients in the product
- Boxed warning(s): none reported

Vigabatrin (Sabril)

- Boxed warnings: Permanent vision loss
  - Sabril can cause permanent bilateral concentric visual field constriction, including tunnel vision that can result in disability. In some cases, Sabril may also decrease visual acuity.
  - Risk increases with increasing dose and cumulative exposure, but there is no dose or exposure to Sabril known to be free of risk of vision loss.
  - Risk of new and worsening vision loss continues as long as Sabril is used, and possibly after discontinuing Sabril.
  - Baseline and periodic vision assessment is recommended for patients on Sabril. However, this assessment cannot always prevent vision damage.
  - Because of the risk of permanent vision loss, Sabril is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Vigabatrin REMS Program. Further information is available at www.vigabatrinrems.com.

Clobazam (Onfi)

- Contraindication(s): history of hypersensitivity to the drug or its ingredients
- Boxed warning(s): risks from concomitant use with opioids; abuse, misuse, and addiction; dependence and withdrawal reactions

Pregablin (Lyrica, Lyrica CR)

- Contraindication(s): known hypersensitivity to pregabalin or any of its components
- Boxed warning(s): none reported

Rufinamide (Banzel)

- Contraindication(s): Banzel is contraindicated in patients with familial short QT syndrome.
- Boxed warning(s): None reported

Midazolam (Nazilyam)

- Contraindication(s): acute narrow-angle glaucoma; hypersensitivity to midazolam
- 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.
    - DS, also called severe myoclonic epilepsy of infancy, is a severe form of epilepsy. Per the United Kingdom National Institute for Health and Care Excellence (NICE) Anti-Epileptic Pharmacologic Treatment Guidelines (published on January 2012 and updated on April 2018), the recommended first-line anti-epileptic drugs to treat DS are sodium valproate and topiramate. Clobazam and stiripentol are listed as adjunctive anti-epileptic drugs. Except for stiripentol, these drugs are not FDA-approved for treatment of DS.
    - LGS is another severe form of epilepsy. Per American Academy of Neurology and the American Epilepsy Society Anti-Epileptic Pharmacologic Treatment Guidelines, the recommended treatment for drop seizures associated with LGS is lamotrigine and topiramate (Level A).

      A Cochrane Database of Systematic Review 2013 article concluded that the optimum treatment for LGS remains uncertain and no study to date has shown any one drug to be highly efficacious; rufinamide, lamotrigine, topiramate and felbamate may be helpful as add-on therapy, and clobazam may be helpful for drop seizures. Until further research has been undertaken, clinicians will need to continue to consider each patient individually, taking into account the potential benefit of each therapy weighed against the risk of adverse effects.
    - Seizures associated with TSC are a rare neurocutaneous genetic disorder, with a prevalence of one in 6,000 to 10,000. Mutations in either TSC1 or TSC2 lead to over-activation of the mammalian target of rapamycin (mTOR) pathway and relatively uncontrolled cell growth that causes growth of benign tumors (hamartomas) in various organs, such as the brain, kidneys, skin, heart, lungs and bones, with epilepsy being the most common neurological symptom in TSC. While vigabatrin is the recommended first-line therapy for TSC-associated infantile spasms, anticonvulsant therapy of other seizure types in TSC should generally follow that of other epilepsies per the Tuberous Sclerosis Complex Surveillance and Management Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference and the 2019 UK guidelines for management and surveillance of TSC. Patients with TSC can present with almost any seizure type including tonic, atonic or tonic-clonic seizures, with about two-thirds having refractory focal-onset (previously referred to as partial-onset) epilepsy; focal seizures and epileptic spasms are the most prevalent.
- Dravet syndrome, also known as severe myoclonic epilepsy of infancy (SMEI), is a severe form of epilepsy with an incidence of 1 in 15,700 to 1 in 40,900. Diagnosis is largely based on clinical presentation as magnetic resonance imaging (MRI) is usually normal and electroencephalography (EEG) findings are nonspecific.

- Complete seizure control is typically not achievable, so the primary goal of therapy is to reduce seizure frequency. The following therapies are recommended for the management of Dravet syndrome by the United Kingdom National Institute for Health and Care Excellence (NICE; April 2018) and a North American Consensus Panel (January 2017):

	NICE	North American Consensus Panel
1st line	Valproic acid or topiramate	Valproic acid or clobazam *If first choice is not effective, then add the other*
2nd line	Addition of clobazam or Diacomit	Addition of Diacomit or topiramate
3rd line	Refer to tertiary specialist	Addition of clonazepam, levetiracetam, zonisamide, ethosuximide, or phenobarbital

- Diacomit increases plasma concentrations of clobazam through inhibition of CYP3A4 and 2C19.
- FDA-approved in August 2018, Diacomit had long prior been used in clinical practice in Canada, Japan, and European countries as well as off-label in the United States through a compassionate-use program.
    - 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.

IV. Dosage and Administration

Cannabidiol (Epidiolex)

Indication	Dosing Regimen	Maximum Dose
DS, LGS	Initial dose is 2.5 mg/kg PO BID (5 mg/kg/day). Maintenance dose is 5 mg/kg PO BID (10 mg/kg/day) to 10 mg/kg PO BID (20 mg/kg/day). Dosage adjustment is recommended for patients with moderate or severe hepatic impairment.	20 mg/kg/day
TSC	Initial dose is 2.5 mg/kg PO BID (5 mg/kg/day). Increase the dose in weekly increments of 2.5 mg/kg PO BID (5 mg/kg/day), as tolerated, to a recommended maintenance dosage of 12.5 mg/kg PO BID (25 mg/kg/day). For patients in whom a more rapid titration to 25 mg/kg/day is warranted, the dosage may be increased no more frequently than every other day.	25 mg/kg/day

Clobazam (Onfi)

LGS	Patients ≤ 30 kg body weight: initiate at 5 mg PO daily and titrate as tolerated up to 20 mg daily Patients > 30 kg body weight: initiate at 10 mg PO daily and titrate as tolerated up to 40 mg daily A daily dose of Onfi greater than 5 mg should be administered in divided doses twice daily; a 5 mg daily dose can be administered as a single dose.	≤ 30 kg body weight: 20 mg/day > 30 kg body weight: 40 mg/day
Intractable/refractory epilepsy (off-label)	See LGS	See LGS
Dravet syndrome (off-label)	Initial: 0.2-0.3 mg/kg/day PO Maximum: 0.5-2 mg/kg/day PO	See regimen

Lacosamide (Motpoly XR, Vimpat)

Drug Name	Indication	Dosing Regimen	Maximum Dose
Immediate-release lacosamide (Vimpat)	Partial-onset seizures, primary generalized tonic-clonic seizures	*Adults (17 years and older):* Initial dosage for monotherapy is 100 mg PO or IV BID; Initial dosage for adjunctive therapy is 50 mg PO or IV BID. *Pediatric patients 1 month old to < 17 years old*: The recommended dosage is based on body weight and is administered PO BID or IV TID.	*Adults (17 years and older):* 400 mg/day *Pediatric patients 4 Years to less than 17 years*: ≥ 50 kg: 400 mg/day 30 kg to < 50 kg: 8 mg/kg/day 6 kg to < 30 kg: 12 mg/kg/day < 6 kg: 15 mg/kg/day
Extended-release lacosamide (Motpoly XR)	Partial-onset seizures, primary generalized tonic-clonic seizures	*Adults (17 years and older):* Initial dosage for monotherapy is 200 mg PO QD; Initial dosage for adjunctive therapy is 100 mg PO QD. *Pediatric patients weighing ≥ 50 kg*:	*Adults (17 years and older):* 400 mg/day *Pediatric patients weighing ≥ 50 kg*: 400 mg/day

Drug Name	Indication	Dosing Regimen	Maximum Dose
		Initial dosage is 100 mg PO QD.	

Midazolam

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

Pregablin (Lyrica, Lyrica CR)

Drug Name	Availability
Pregabalin (Lyrica)	Capsules: 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg Oral solution: 20 mg/mL
Pregabalin extended-release (Lyrica CR)	Tablets: 82.5 mg, 165 mg, 330 mg

Rufinamide (Banzel)

Indication	Dosing Regimen	Maximum Dose
LGS	• *Pediatric patients 1 year to less than 17 years:* Starting daily dose: Film-coated tablets: 200 mg, 400 mg Oral suspension: 40 mg/mL 10 mg/kg per day in two equally divided doses; increase by 10 mg/kg increments every other day to maximum dose of 45 mg/kg per day, not to exceed 3200 mg per day, in two divided doses *Adults (17 years and older):* Starting daily dose: 400-800 mg per day in two equally divided doses; increase by 400-800 mg every other day until a maximum dose of 3200 mg per day, in two divided doses, is reached	3200 mg/day

Stiripentol (Diacomit)

Indication	Dosing Regimen	Maximum Dose
Dravet syndrome	Age ≥ 6 months and weighing 7 kg to < 10 kg: 25 mg/kg twice daily	50 mg/kg/day (not to exceed 3,000 mg/day)

Indication	Dosing Regimen	Maximum Dose
	Age ≥ 1 year and weighing ≥ 10 kg: 25 mg/kg twice daily or 16.67 mg/kg three times daily	

Vigabatrin (Sabril)

Indication	Dosing Regimen	Maximum Dose
Infantile spasms	50 mg/kg/day (25 mg/kg PO BID); increase total daily dose in increments of 25 mg/kg/day PO every 3 days to 50 mg/kg/day	150 mg/kg/day (75 mg/kg twice daily)
Complex partial seizures	Adults (> 17 years): 1,000 mg/day (500 mg PO BID); increase total daily dose weekly in 500 mg/day increments to 3,000 mg/day Pediatrics (2-16 years): 500 mg/day (250 mg PO BID); increase total daily dose weekly in 500 mg/day increments to 2,000 mg/day; Patients weighing more than 60 kg should be dosed according to adult recommendations.	Adults: 3000 mg/day (1,500 mg twice daily) Pediatrics: 2,000 mg/day (1,000 mg twice daily)

Diazepam nasal spray (Valtoco)

<table>
<tr><th>Indication</th><th>Dosing Regimen</th><th>Maximum Dose</th></tr>
<tr><td>Seizure clusters in</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>
</table></td><td>2 doses/single episode; do not treat more than 1 episode every 5</td></tr>
</table>

patients with epilepsy	56-74	≥ 76	20	Two 10 mg devices	1 spray in each nostril	days or more than 5 episodes/month

V. Product Availability

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

Epidolox: Oral solution: 100 mg/mL (100 mL)

Lacosamide:

Drug Name	Availability
Immediate-release lacosamide (Vimpat)	• Tablets: 50 mg, 100 mg, 150 mg, 200 mg • Oral solution: 10 mg/mL (200 mL) • Single-dose vial for intravenous use: 200 mg/20 mL
Extended-release lacosamide (Motpoly XR)	Capsules: 100 mg, 150 mg, 200 mg

Midazolam

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

Sabril: Tablet: 500 mg , Powder for oral solution: 500 mg

Clobazam:

Drug Name	Availability
Clobazam (Onfi)	Tablet with a functional score: 10 mg, 20 mg Oral suspension: 2.5 mg/mL in 120 mL bottles
Clobazam (Sympazan)	Oral film: 5 mg, 10 mg, 20 mg

Rufinamide (Banzel)

- Film-coated tablets: 200 mg, 400 mg
- Oral suspension: 40 mg/mL

Stiripentol

- Capsules: 250 mg, 500 mg
- Powder for oral suspension: 250 mg, 500 mg

VI. References

Clobazam

1. Onfi Prescribing Information. Deerfield, IL: Lundbeck; February 2020. Available at: https://www.onfihcp.com/. Accessed August 20, 2021..
2. Sympazan Prescribing Information. Warren, NJ: Aquestive Therapeutics; March 2021. Available at: www.sympazan.com. Accessed August 20, 2021.
3. Hancock EC, Cross JH. Treatment of Lennox-Gastaut syndrome. Cochrane Database Syst Rev. 2013 Feb 28;(2).
4. Arzimanoglou A, French J, Blume WT, et al. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. Lancet Neurol. 2009 Jan;8(1):82-93.
5. Mills JK, Lewis TG, Mughal K, et al. Retention rate of clobazam, topiramate and lamotrigine in children with intractable epilepsies at 1 year. Seizure. 2011 June;20(5): 402-405.

6. Gauthier AC, Mattson RH. Clobazam: a safe, efficacious, and newly rediscovered therapeutic for epilepsy. CNS Neurosci Ther. 2015 Jul;21(7):543-8.
7. Montenegro MA, Arif H, Nahm EA, et al. Efficacy of clobazam as add-on therapy for refractory epilepsy: experience at a US epilepsy center. Clin Neuropharmacol. 2008 NovDec;31(6):333-8.
8. Cross JH, Auvin S, Falip M, et al. Expert Opinion on the Management of Lennox–Gastaut Syndrome: Treatment Algorithms and Practical Considerations. Frontiers in Neurology. 2017;8:505.
9. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2018. Available at: http://www.clinicalpharmacology-ip.com/. Accessed August 420, 2021.
10. Wirrell EC, Laux L, Jette N, et al. Optimizing the diagnosis and management of Dravet syndrome: recommendations from a North American consensus panel. Pediatr Neurol. 2017; 68: 18-34.
11. Epilepsies: diagnosis and management. National Institute for Health and Care Excellence (NICE) website. https://www.nice.org.uk/guidance/CG137/chapter/Appendix-EPharmacological-treatment. Updated April 2018. Accessed August 22, 2018.
12. Wirrell EC. Treatment of Dravet syndrome. Can J Neurol Sci. 2016; 43 Suppl 3: S13-8. doi: 10.1017/cjn.2016.249. https://www.ncbi.nlm.nih.gov/pubmed/27264138.
13. Practice Guideline Update: Efficacy and Tolerability of the New Antiepileptic Drugs II: Treatment-resistant Epilepsy. American Academy of Neurology. Available at: https://www.aan.com/Guidelines/Home/GetGuidelineContent/922. Accessed July 25, 2019.

Valtoco

1. Valtoco Prescribing Information. San Diego, CA: Neurelis, Inc.; February 2022. Available at: https://www.valtoco.com. Accessed August 25, 2022.
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.

5. Schachter SC. Seizure clusters. Available at: https://www.epilepsy.com/learn/professionals/refractory-seizures/potentially-remediable-causes/seizure-clusters. Accessed October 3, 2019.
6. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed August 25, 2022.

Epidioloex

14. Epidiolex Prescribing Information. Carlsbad, CA: Greenwich Biosciences, Inc; January 2023. Available at: https://pp.jazzpharma.com/pi/epidiolex.en.USPI.pdf. Accessed May 18, 2023.
15. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2020. Available at: http://www.clinicalpharmacology-ip.com/.
16. National Institute of Neurological Disorders and Stroke. Dravet Syndrome Information Page. Available at: https://www.ninds.nih.gov/Disorders/All-Disorders/Dravet-Syndrome-Information-Page.
17. Wirrell EC. Treatment of Dravet syndrome. Can J Neurol Sci. 2016 Jun;43 Suppl 3:S13-8.

18. National Institute for Health and Care Excellance (NICE). Epilepsies: diagnosis and management. Available at: https://www.nice.org.uk/guidance/CG137/chapter/Appendix-E-Pharmacological-treatment.
19. Ferrie CD, Patel A. Treatment of Lennox-Gastaut syndrome. Eur J Paediatr Neurol. 2009 Nov;13(6):493-504.
20. Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment resistant epilepsy. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. July 10, 2018; 91 (2).
21. National Institute of Neurological Disorders and Stroke. Lennox-Gastaut Syndrome Information Page. Available at: https://www.ninds.nih.gov/Disorders/All-Disorders/Lennox-Gastaut-Syndrome-Information-Page.
22. Panebianco M, Prabhakar H, Marson AG. Rufinamide add-on therapy for refractory epilepsy. Cochrane Database of Systematic Reviews 2018, Issue 4. Art. No.: CD011772.
23. Hancock EC, Cross JH. Treatment of Lennox-Gastaut syndrome. Cochrane Database of Systematic Reviews 2013, Issue 2. Art. No.: CD003277.
24. Kim HJ, Kim SH, MD, Kang HC, et al. Adjunctive Levetiracetam Treatment in Pediatric Lennox-Gastaut Syndrome. Pediatr Neurol. 2014 Oct;51(4):527-31. doi: 10.1016/j.pediatrneurol.2014.06.004. Epub 2014 Jun 25. https://www.ncbi.nlm.nih.gov/pubmed/25266616.
25. Grosso S, Franzoni E, Coppola G, et al. Efficacy and safety of levetiracetam: an add-on trial in children with refractory epilepsy. Seizure. 2005 Jun;14(4):248-53. https://www.ncbi.nlm.nih.gov/pubmed/15911359.
26. Asadi-Pooya AA. Lennox-Gastaut syndrome: a comprehensive review. Neurol Sci. 2018 Mar;39(3):403-414. doi: 10.1007/s10072-017-3188-y. Epub 2017 Nov 9. https://www.ncbi.nlm.nih.gov/pubmed/29124439.
27. Amin S, Kingswood JC, Bolton PF, et al. The UK guidelines for management and surveillance of Tuberous Sclerosis Complex. QJM: An International Journal of Medicine. 2019;112(3):171–182.
28. Krueger DA, Northrup H, et al. Tuberous sclerosis complex surveillance and management: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol. 2013;49(4):255-65.

Vigabatrin (Sabril)

1. Sabril Prescribing Information. Deerfield, IL: Lundbeck. October 2021. Available at https://www.sabril.net/prescribing-sabril. Accessed April 19, 2023.
2. Hancock EC, Osborne JP, Edwards SW. Treatment of infantile spasms. Cochrane Epilepsy Group – Cochrane Database of Syst Rev. June 5, 2013; 6: CD001770. doi: 10.1002/14651858.CD001770.pub3.
3. Pellock JM, Hrachovy R, Shinnar S, et al. Infantile spasms: A U.S. consensus report. Epilepsia. October 2010; 51(10): 2175-89. doi: 10.1111/j.1528-1167.2010.02657.x.
4. Go CY, Mackay MT, Weiss SK, et al. Evidence-based guideline update: Medical treatment of infantile spasms. Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. June 12, 2012; 78(24): 1974-80. doi: 10.1212/WNL.0b013e318259e2cf.
5. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2018. Available at: http://www.clinicalpharmacology-ip.com/. Accessed April 20, 2021.

6. Kanner AM, et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset epilepsy. Neurology 2018;91:74-81.
7. Kanner AM, et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs II: treatment-resistant epilepsy. Neurology 2018;91:82-90.

Lacosamide (Motpoly XR, Vimpat)

1. Vimpat Prescribing Information. Smyrna, GA: UCB, Inc.; October 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022253s049,022254s039,022255s031lbl.pdf. Accessed December 9, 2021.
2. Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset epilepsy. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. July 10, 2018; 91(2):74-81.
3. Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment resistant epilepsy. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Epilepsy Curr. Jul-Aug 2018;18(4):269-78.

Midazolam (Nayzilam)

1. Nayzilam Prescribing Information. Smyrna, GA: UCB Biopharma SPRL; January 2023. Available at: https://www.nayzilam.com/. Accessed May 14, 2024.
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.
3. Kumar A. Complex partial seizure. Available at: https://www.ncbi.nlm.nih.gov/books/NBK519030/.
4. Schachter SC. Seizure clusters. Available at: https://www.epilepsy.com/learn/professionals/refractory-seizures/potentially-remediable-causes/seizure-clusters.
5. Holsti M, Dudley N, Schunk J, et al. Intranasal midazolam vs rectal diazepam for the home treatment of acute seizures in pediatric patients with epilepsy. Arch Pediatr Adolesc Med. 2010;164:747-753. Available at: https://jamanetwork.com/journals/jamapediatrics/fullarticle/383593.
6. Detyniecki K, Van Ess PJ, Sequeira DJ, et al. Safety and efficacy of midazolam nasal spray in the outpatient treatment of patients with seizure clusters. John Wiley & Sons, Inc. 2019; 00:1–12. https://doi.org/10.1111/epi.15159.
7. Goodman S, Chan G, Gunawardane NA, et al. Acute management of seizure clusters and prolonged seizures: a review of rescue therapies. TouchReviews in Neurology. 2024;20(1):4-9.
8. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed June 5, 2024.

Pregablin (Lyrica, Lyrica CR)

1. Lyrica Prescribing Information. New York, NY: Pfizer Inc.; June 2020. Available at: http://labeling.pfizer.com/showlabeling.aspx?id=561. Accessed February 9, 2023.
2. Lyrica CR Prescribing Information. New York, NY: Pfizer Inc.; June 2020. Available at: http://labeling.pfizer.com/ShowLabeling.aspx?id=9678. Accessed February 9, 2023.
3. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2023. Available at: https://www.clinicalkey.com/pharmacology/. Accessed February 22, 2023.

Rufinamide (Banzel)

1. Banzel Prescribing Information. Woodcliff Lake, NJ: Eisai Inc.; December 2021. Available at: https://www.banzel.com/. Accessed April 19, 2023.
2. Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset epilepsy. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. July 10, 2018;91(2):74-81.
3. Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment resistant epilepsy. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. July 10, 2018;91(2):82-90.
4. Hancock EC, Cross JH. Treatment of Lennox-Gastaut syndrome. Cochrane Database Syst Rev. 2013 Feb 28;(2):CD003277.
5. Arzimanoglou A, French J, Blume WT, et al. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. Lancet Neurol. 2009 Jan;8(1):82-93.
6. Cross JH, Auvin S, Falip M, et al. Expert opinion on the management of Lennox–Gastaut Syndrome: treatment algorithms and practical considerations. Frontiers in Neurology. 2017;8:505.
7. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2018. Available at: http://www.clinicalpharmacology-ip.com. Accessed March 16, 2021.
8. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed May 18, 2023.
9. Chin RF, Mingorance A, Ruban-Fell B, et al. Treatment guidelines for rare, early-onset, treatment-resistant epileptic conditions: a literature review on Dravet syndrome, Lennox-Gastaut syndrome and CDKL5 deficiency disorder. Frontiers in Neurology. Oct 2021;12:734612. doi: 10.3389/fneur.2021.734612.

Stiripentol

1. Diacomit Prescribing Information. Beauvais, France: Biocodex; July 2022. Available at: www.diacomit.com/downloads/pdf/DIACOMIT_US_PI.pdf. Accessed July 5, 2023.

2. Wirrell EC, Laux L, Jette N, et al. Optimizing the diagnosis and management of Dravet syndrome: recommendations from a North American consensus panel. Pediatr Neurol. 2017; 68:18-34.
3. National Institute for Health and Care Excellence (NICE). Epilepsies: diagnosis and management. Available at: https://www.nice.org.uk/guidance/CG137/chapter/Appendix-E-Pharmacological-treatment. Accessed August 1, 2019.
4. Wirrell EC, Hood V, Knupp KG et al. International consensus on diagnosis and management of Dravet syndrome. Epilepsia. 2022;63:1761-77. DOI: 10.1111/epi.17274.
5. Strzelczyk A, Schubert-Bast S. A practical guide to the treatment of Dravet syndrome with anti-seizure medication. CN Drugs. 2022;36:217–237. https://doi.org/10.1007/s40263-022-00898-1.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created: adapted from previously approved individual drug policies – CP.PMN.184 Diacomit, MDN.CP.PMN.164 Epidiolex, MDN.CP.PMN.54 Clobazam, CP.PMN.211 Midazolam, MDN.CP.PMN.157 Rufinamide, MDN.CP.PMN.216 Valtoco, MDN.CP.PHAR.169 Sabril, MDN.CP.PMN.33 Lyrica, MDN.CP.PMN.155 Lacosamide for migration to HFS PDL	10.3.24	

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.