Clinical Policy Title:	clobazam
Policy Number:	RxA.429
Drug(s) Applied:	Onfi®, Sympazan®
Original Policy Date:	03/06/2020
Last Review Date:	09/14/2021
Line of Business Policy Applies to:	All lines of business

Background

Clobazam (Onfi®, Sympazan®) is a benzodiazepine. Onfi® and Sympazan® are indicated for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age or older.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
clobazam (Onfi®, Sympazan®)	LGS	**Patients ≤ 30 kg body weight:** initiate at 5 mg orally daily and titrate as tolerated up to 20 mg daily. With mild to moderate hepatic impairment (Child-Pugh score 5 to 9): Initiate dosing at 5 mg orally once daily and titrate to 5 mg orally twice daily on Day 14, then 10 mg orally twice daily on Day 21, as tolerated.* **Patients > 30 kg body weight:** initiate at 10 mg orally daily and titrate as tolerated up to 40 mg daily. With mild to moderate hepatic impairment (Child-Pugh score 5 to 9): Initiate dosing at 5 mg orally once daily and titrate to 5 mg orally twice daily on Day 7, 10 mg orally twice daily on Day 14, then 20 mg orally twice daily on Day 21, as tolerated.* 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

* Dosage Adjustments in Geriatric Patients: The starting dosage should generally be 5 mg/day for all geriatric patients. Then proceed slowly with dose escalation; titrate according to weight, but to half the dosage presented in above table, as tolerated. If necessary and based upon clinical response, an additional titration to the maximum dosage (20 mg/day

or 40 mg/day, depending on weight) may be started on day 21.
Dosage Adjustments in CYP2C19 Poor Metabolizers: Same as in geriatric patients.

Dosage Forms

- clobazam (Onfi®): Tablet with a functional score: 10 mg, 20 mg
  Oral suspension: 2.5 mg/mL in 120 mL bottles
- clobazam (Sympazan®): Film: 5 mg, 10 mg, 20 mg

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. Lennox-Gastaut Syndrome (must meet all)**:**

1. Diagnosis of LGS;
2. Prescribed by or in consultation with a neurologist;
3. Age ≥ 2 years;
4. Failure of two preferred agents for LGS (e.g., clonazepam, valproic acid [divalproex], lamotrigine, topiramate, felbamate), unless all are contraindicated, or clinically significant adverse effects are experienced;
5. For Onfi® and Sympazan® requests, medical justification supports the inability to use generic clobazam tablets and oral suspension (e.g., contraindications to excipients in generic formulations);
6. Dose does not exceed 40 mg per day.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

B. Intractable/Refractory Epilepsy (off-label) (must meet all)**:**

1. Diagnosis of intractable/refractory epilepsy;
2. Prescribed by or in consultation with a neurologist;
3. Age ≥ 2 years;
4. Failure of ≥ 4 anti-seizure drugs (see Appendix B), unless all are contraindicated or clinically significant adverse effects are experienced;
5. For Onfi® and Sympazan® requests, medical justification supports the inability to use generic clobazam tablets and oral suspension (e.g., contraindications to excipients in generic formulations);
7. Dose does not exceed 40 mg per day.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

C. Dravet Syndrome (off-label) (must meet all)**:**

1. Diagnosis of Dravet syndrome;
2. Prescribed by or in consultation with a neurologist;
3. Age ≥ 2 years;
4. For Onfi® and Sympazan® requests, medical justification supports the inability to use generic clobazam

tablets and oral suspension (e.g., contraindications to excipients in generic formulations);
5. Dose does not exceed 2 mg/kg per day.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

II. Continued Therapy Approval

A. All Indications in Section I (must meet all)**:**

1. Member is currently receiving medication that has been authorized by RxAdvance, or documentation supports that member is currently receiving Onfi® or Sympazan® for Lennox-Gastaut syndrome, intractable/ refractory epilepsy, or Dravet syndrome 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 one of the following (a or b):
   a. LGS or intractable/refractory epilepsy: 40 mg per day;
   b. Dravet syndrome: 2 mg/kg per day.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
LGS: Lennox-Gastaut syndrome
CNS: Central Nervous System

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
Anticonvulsants-benzodiazepines		
clonazepam (Klonopin®)	Adult: 1.5 mg/day orally, divided into 3 equal doses 11 to 17 years: 1.5 mg/day orally Infants and Children ≤ 10 years: 0.01 to 0.03 mg/kg/day orally	Adult: 20 mg/day orally Adolescents > 30 kg: 20 mg/day orally < 30kg: 0.1 to 0.2 mg/kg/day orally Children & Infants: 0.1 to 0.2 mg/kg/day orally
diazepam (Diastat®)	Adult: 2 to 10 mg orally 2 to 4 times 6 months to 17 years: 1 to 2.5 mg orally 3 to 4 times daily	40 mg/day orally Adolescent & Children: 0.6 mg/kg intravenous in 8 hour
Carbamates		

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
felbamate (Felbatol®)	15 mg/kg/day orally in 3—4 divided doses. Increase felbamate dosage by 15 mg/kg/day increments at weekly intervals to 45 mg/kg/day orally.	3600 mg/day
GABA modulators		
vigabatrin (Sabril®)	1,500 mg orally twice daily	3,000 mg/day orally
tiagabine (Gabitril®)	Adult: 4 mg/day orally Adolescents ≥ 4 mg/day orally Children: 2-11 years: 0.1 mg/kg/day orally	Adult: 56 mg/day orally Adolescents ≥ 12 years: 32 mg/day orally Children: 2-11 years: 0.6—1 mg/kg/day orally
Hydantoins		
phenytoin (Dilantin®)	Adult: 15 to 20 mg/kg/dose intravenous Infants, Children, and Adolescents: 20 mg/kg/dose intravenous Neonates: 15 to 20 mg/kg/dose intravenous	Varies
Succinimides		
ethosuximide (Zarontin®)	Adults, Adolescents, and Children > 6 years: 250 mg orally twice daily Children 3-6 years: 15 mg/kg/day orally	Adults & Adolescent: 1.5 g/day orally Children > 6 years: 1.5 g/day orally 3-6 years: NA
Celontin®	Adults: 300 mg orally daily Adolescents and Children: 10—15 mg/kg orally	Adults: 1.2 g/day orally Adolescents & Children: 30 mg/kg/day orally
Valproic acid		
divalproex sodium (Depakote®)	See full prescribing information	See full prescribing information
valproic acid	10 to 15 mg/kg/day orally	60 mg/kg/day orally
AMPA glutamate receptor antagonists		
Fycompa®	2mg orally	12 mg/day orally.
Anticonvulsants-miscellaneous		
Briviact®, carbamazepine	See full prescribing	See full prescribing information

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
(Tegretol®, Tegretol XL®), Aptiom®, gabapentin (Neurontin®), Vimpat® ’lamotrigine (Lamictal®), levetiracetam (Keppra®, Spritam®), oxcarbazepine (Trileptal®, Oxtellar XR®), pregabalin (Lyrica®), primidone (Mysoline®), rufinamide (Banzel®), topiramate (Topamax®, Qudexy XR®, Trokendi XR®), zonisamide (Zonegran®)	information	

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):
  - History of hypersensitivity to the drug or its ingredients.

- Boxed Warning(s):
  - Onfi® and Sympazan®: Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.
  - The use of benzodiazepines, including Onfi®, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Before prescribing Onfi® and throughout treatment, assess each patient’s risk for abuse, misuse, and addiction.
  - Abrupt discontinuation or rapid dosage reduction of Onfi® after continued use may precipitate acute withdrawal reactions, which can be life-threatening. To reduce the risk of withdrawal reactions, use a gradual taper to discontinue Onfi® or reduce the dosage.

APPENDIX D: General Information

- Somnolence or Sedation: Monitor for central nervous system (CNS) depression. Risk may be increased with concomitant use of other CNS depressants.
- Withdrawal: Symptoms may occur with rapid dose reduction or discontinuation. Discontinue Sympazan® gradually.
- Serious Dermatological Reactions (including Stevens-Johnson Syndrome and toxic epidermal necrolysis): Discontinue Sympazan® at first sign of rash unless the rash is clearly not drug-related.
- Physical and Psychological Dependence: Monitor patients with a history of substance abuse for signs of habituation and dependence.
- Suicidal Behavior and Ideation: Monitor for suicidal thoughts or behaviors.

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 table updated. 2. Initial Therapy and Continued Therapy Approval duration updated from length of benefit to 12 months for commercial and for HIM updated to 12 months for Onfi® and Sympazan® both	07/30/2020	09/14/2020

3. Continued Therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance..." 4. Reference reviewed and updated.		
Policy was reviewed. 1. Dosing Information dosing regimen was updated to include hepatic impairment dosing, “With mild to moderate hepatic impairment (Child-Pugh score 5 to 9): Initiate dosing…”. 2. Dosing Information was updated to remove off label indications “Intractable/refractory epilepsy” and “Dravet Syndrome”. 3. Statement about provider sample ‘‘The provision of provider samples does not guarantee coverage…” was added to Clinical Policy. 4. Initial Approval Crtieria and Continued Therapy Approval Criteria were updated to remove HIM approval duration.. 5. Continued Therapy Approval Criteria II.A.1 was rephrased to “Member is currently receiving medication that has been authorized by RxAdvance…”. 6. Appendix A was updated to include abbreviation CNS. 7. Therapeutic alternative verbiage was updated to "Below are suggested therapeutic alternatives based on clinical guidance..". 8. Appendix B was updated to include specific dosing regimen and maximum dose for clonazepam, “Adult: 1.5 mg/day orally, divided into 3 equal…”. 9. Appendix B was updated to include specific dosing regimen and maximum dose for diazepam, “Adult: 2 to 10 mg orally 2 to 4 times…”. 10. Appendix B was updated to include specific dosing regimen and maximum dose for vigabatrin, “1,500 mg orally twice daily…”. 11. Appendix B was updated to include specific dosing regimen and maximum dose for tiagabine, “Adult: 4 mg/day orally…” 12. Appendix B was updated to remove Peganone and its dosing information due to inactive status of the drug. 13. Appendix B was updated to include specific	07/05/2021	09/14/2021

dosing regimen and maximum dose for phenytoin, “Adult: 15 to 20 mg/kg/dose…”. 14. Appendix B was updated to include specific dosign regimen and maximum dose for Celontin, “Adults: 300 mg orally daily…”. 15. Appendix B was updated to include specific dosing regimen and maximum dose for valproic acid, “10 to 15 mg/kg/day orally…”. 16. Appendix B was updated to include specific dosing regimen and maximum dose for Vycompa, “2mg orally…”. 17. Appendix B was updated to include specific dosing regimen and maximum dose for ethosuximide, “Adults, Adolescents, and Children…”. 18. Appendix B was updated to remove the following inactive/unavailable brand-name drugs: Peganone, Depakene, and Potiga. 19. Appendix B was updated to remove the following inactive/unavailable generic drugs: ethotoin, perampanel, brivaracetam, eslicarbazepine, ezogabine, lacosamide, rufinamide, and methsuximide. 20. Statement about drug listing format in Appendix B is updated 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". 21. Appendix C was updated to include Boxed Warnings, “Onfi® and Sympazan®: Concomitant use of benzodiazepines…”, “The use of benzodiazepines, including Onfi®, exposes users to risks of abuse…”, and “Abrupt discontinuation or rapid dosage reduction of Onfi® after continued use…”. 22. Appendix D was updated to include several warnings and precautions, “Somnolence or Sedation…”, “Withdrawal: Symptoms may occur…”, “Serious Dermatological Reactions (including Stevens-Johnson Syndrome and toxic epidermal necrolysis)…”, “Physical and Psychological Dependence: Monitor patients…”, and “Suicidal Behavior and Ideation: Monitor…”.		

23. References were reviewed and updated.		