Clinical Policy: Gabapentin ER (Gralise, Horizant)

Reference Number: CP.PMN.240
Effective Date: 09.01.20
Last Review Date: 08.25
Line of Business: Commercial, HIM, Medicaid

Revision Log

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

Description

Gabapentin (Gralise®) is an analog of gamma-aminobutyric acid (GABA) that has GABA agonist activity.

Gabapentin enacarbil ER (Horizant®) is a prodrug of gabapentin.

FDA Approved Indication(s)

Gralise and Horizant are indicated for the management of postherpetic neuralgia (PHN).

Horizant is also indicated for the treatment of moderate-to-severe primary restless legs syndrome (RLS) in adults.

Limitation(s) of use:

- Horizant is not recommended for patients who are required to sleep during the daytime and remain awake at night.
- Gralise and Horizant are not interchangeable with other gabapentin products because of differing pharmacokinetic profiles that affect the frequency of administration.

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 Gralise and Horizant are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Postherpetic Neuralgia (must meet all)**:**

1. Diagnosis of PHN;
2. Age ≥ 18 years;
3. Failure of a ≥ 30 day trial of immediate-release generic gabapentin at ≥ 1,800 mg per day, unless contraindicated to its excipients or clinically significant adverse effects are experienced;*
   **For Illinois HIM requests, the step therapy requirements above do not apply as of 1/1/2026 per IL HB 5395*
4. Failure of a ≥ 30-day trial of generic pregabalin^ (immediate-release or controlled-release) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;*
   **Prior authorization may be required for pregabalin*

**For Illinois HIM requests, the step therapy requirements above do not apply as of 1/1/2026 per IL HB 5395*

5. If member is ≤ 64 years of age: Failure of a ≥ 30-day trial of a tricyclic antidepressant (TCA) (e.g., amitriptyline, nortriptyline, imipramine) at up to maximally indicated doses, clinically significant adverse effects are experienced, or all are contraindicated;*
   **For Illinois HIM requests, the step therapy requirements above do not apply as of 1/1/2026 per IL HB 5395*
6. For Gralise requests, member must use generic once-daily gabapentin, if available, unless contraindicated or clinically significant adverse effects are experienced;
7. Dose does not exceed (a or b):
   a. Gralise (i and ii):
      i. 1,800 mg per day;
      ii. 2 tablets per day;
   b. Horizant (i and ii):
      i. 1,200 mg per day;
      ii. 2 tablets per day.

Approval duration:
Medicaid/HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

B. Restless Leg Syndrome (must meet all)**:**

1. Diagnosis of RLS;
2. Request is for Horizant;
3. Age ≥ 18 years;
4. Failure of a ≥ 30 day trial of immediate-release generic gabapentin at up to maximally indicated doses, unless contraindicated to its excipients or clinically significant adverse effects are experienced;*
   **For Illinois HIM requests, the step therapy requirements above do not apply as of 1/1/2026 per IL HB 5395*
5. Failure of a ≥ 30-day trial of generic pregabalin^ (immediate-release or controlled-release) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;*
   ^Prior authorization may be required for pregabalin
   **For Illinois HIM requests, the step therapy requirements above do not apply as of 1/1/2026 per IL HB 5395*
6. Dose does not exceed (a and b):
   a. 600 mg per day;
   b. 1 tablet per day.

Approval duration:
Medicaid/HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

C. 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.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and 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.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and 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.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

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

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member is responding positively to therapy;
3. For Gralise requests, member must use generic once-daily gabapentin, if available, unless contraindicated or clinically significant adverse effects are experienced;
4. If request is for a dose increase, new dose does not exceed (a or b):
   a. PHN (i or ii):
      i. Gralise (1 and 2):
         1) 1,800 mg per day;
         2) 2 tablets per day;
      ii. Horizant (1 and 2):
         1) 1,200 mg per day;
         2) 2 tablets per day;
   b. RLS – Horizant only (i and ii):
      i. 600 mg per day;
      ii. 1 tablet per day.

Approval duration:
Medicaid/HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

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.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and 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.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and 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.CPA.09 for commercial, HIM.PA.154 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.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration
GABA: gamma-aminobutyric acid
PHN: post herpetic neuralgia
RLS: restless legs syndrome
TCA: tricyclic antidepressant

*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	Indication	Dosing Regimen	Dose Limit/ Maximum Dose
gabapentin (Neurontin®)	PHN	300 mg PO as a single dose on day 1, then 600 mg/day (300 mg PO BID) on day 2, and 900 mg/day (300 mg PO TID) on day 3. The dose can then be titrated up as needed for pain relief to a dose of 1,800 mg/day (600 mg PO TID).	1,800 mg/day
	RLS**	300 mg PO QD or 600 mg PO QD and titrated to symptom relief.	3,600 mg/day†
pregabalin (Lyrica®)	RLS**	75 mg PO daily. The dose can be titrated up by 75 mg every week as needed up to 450 mg daily.	450 mg/day
	PHN	75 mg PO BID or 50 mg PO TID. The dose can be titrated up to 300 mg PO BID or 200 mg PO TID for patients who have	600 mg/day†

Drug Name	Indication	Dosing Regimen	Dose Limit/ Maximum Dose
		ongoing pain and are tolerating 300 mg/day.	
pregabalin extended-release (Lyrica CR®)	PHN	165 mg PO QD. The dose can be titrated up to 660 mg PO QD for patients who have ongoing pain and are tolerating 330 mg/day.	660 mg/day
amitriptyline	PHN**	10 to 150 mg PO QHS	150 mg/day†
desipramine (Norpramin®)	PHN**	10 to 25 mg PO QHS and titrate to pain relief as tolerated (in one study, mean dose was 167 mg/day)	200 mg/day†
nortriptyline (Pamelor®)	PHN**	10 mg to 150 mg PO QHS	150 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.
**Agents not included in this list may not have evidence supporting their use in the indications covered by this policy*
***Off-label*
†Maximum dose for drug, not necessarily indication

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): hypersensitivity (Gralise)
- Boxed warning(s): none reported

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
gabapentin ER (Gralise)	PHN	Gralise should be initiated and titrated as follows: Day 1: 300 mg PO Day 2: 600 mg PO Days 3 to 6: 900 mg PO QD Days 7 to 10: 1,200 mg PO QD Days 11 to 14: 1,500 mg PO QD Days ≥ 15: 1,800 mg PO QD	1,800 mg/day
gabapentin enacarbil ER (Horizant)	PHN	600 mg PO QAM for 3 days, then increase to 600 mg PO BID beginning on day 4	1,200 mg/day
	RLS	600 mg PO QD at about 5 PM	600 mg/day

VI. Product Availability

Drug Name	Availability
Gabapentin ER (Gralise)	ER tablets: 300 mg, 450 mg, 600 mg, 750 mg, 900 mg
Gabapentin enacarbil ER (Horizant)	ER tablets: 300 mg, 600 mg

VII. References

1. Gralise Prescribing Information. Morristown, NJ: Almatica Pharma, Inc.; April 2025. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/022544s031lbl.pdf. Accessed May 9, 2025.
2. Horizant Prescribing Information. Woburn, MA; Azurity Pharmaceuticals, Inc.; April 2025. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/022399s014lbl.pdf. Accessed May 9, 2025.
3. Clinical Pharmacology [database online]. Elsevier; 2025. Available at: https://www.clinicalkey.com/pharmacology/. Accessed May 9, 2025.
4. Merative™ Micromedex® Alternative Medicine [Internet database]. Merative, Ann Arbor, Michigan, USA. Available at: https://www.micromedexsolutions.com. Accessed May 9, 2025.

Postherpetic Neuralgia

5. Dubinsky RM, Kabbani H, El-Chami Z, Boutwell C, Ali H. Practice Parameter: Treatment of postherpetic neuralgia. An evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* September 28, 2004 vol. 63 no. 6 959-965.
6. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurology* February 2015; 14(2): 162-173.
7. Saguil A, Kane S, Mercado M, Lauters R. Herpes Zoster and Postherpetic Neuralgia: Prevention and Management. *Am Fam Physician*. 2017 Nov 15;96(10):656-663.
8. Mallick-Searle T, Snodgrass B, Brant JM. Postherpetic neuralgia: epidemiology, pathophysiology, and pain management pharmacology. *J Multidiscip Healthc*. 2016 Sep 21;9:447-454. doi: 10.2147/JMDH.S106340.

Restless Leg Syndrome

9. Silber MH, Buchfuhrer MJ, Earley CJ, et al. The management of restless legs syndrome: an updated algorithm. *Mayo Clinic* July 2021: 96(7): 1921-1937. https://doi.org/10.1016/j.mayocp.2020.12.026.
10. Winkelman JW, Armstrong MJ, Allen RP, et al. Practice guideline summary: Treatment of restless legs syndrome in adults: Report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology. *Neurology*. 2016 Dec 13;87(24):2585-2593. doi: 10.1212/WNL.0000000000003388.
11. Aurora RN, Kristo DA, Bista SR, et al. Update to the AASM Clinical Practice Guideline: "The treatment of restless legs syndrome and periodic limb movement disorder in adults-an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses". *Sleep*. 2012 Aug 1;35(8):1037. doi: 10.5665/sleep.1986.
12. Winkelman JW, Berkowski JA, DelRosso LM, et al. Treatment of restless legs syndrome and periodic limb movement disorder: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med.* 2025 Jan 1;21(1):137-152. doi: 10.5664/jcsm.11390.
13. Winkelman JW, Berkowski JA, DelRosso LM, et al. Treatment of restless legs syndrome and periodic limb movement disorder: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. J Clin Sleep Med. 2025 Jan 1;21(1):153-199. doi: 10.5664/jcsm.11392.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
3Q 2021 annual review: no significant changes; updated reference for HIM off-label use to HIM.PA.154 (replaces HIM.PHAR.21); references reviewed and updated.	05.03.21	08.21
Revised approval duration for Commercial line of business from length of benefit to 12 months or duration of request, whichever is less	09.28.21	02.22
3Q 2022 annual review: updated RLS approval criteria – removed trial of ropinirole and pramipexole, added trial of gabapentin IR and generic pregabalin to align with RLS Foundation clinical guidelines, updated Appendix B: therapeutic alternative table to include.	04.22.22	08.22
Per August SDC and prior clinical guidance, added additional redirection requirements to generic pregabalin immediate and controlled-release and TCA. Template changes applied to other diagnoses/indications and continued therapy section.	08.23.22	11.22
Revised PHN criteria to require trial of pregabalin IR OR ER instead of pregabalin IR AND ER.	12.02.23	02.23
3Q 2023 annual review: no significant changes; for RLS separated redirection requirements for added clarity; RT4: per updated prescribing information added new 450, 750, and 900 mg strengths for Gralise and updated maximum quantity to 2 tablets per day; references reviewed and updated.	04.20.23	08.23
3Q 2024 annual review: for all indications, added asterisk stating that prior authorization may be required for pregabalin, clarified failure of generic gabapentin is required; for PHN, revised wording of age limit for failure of a TCA; in Appendix B, clarified off-label indications and maximum dosing; references reviewed and updated.	05.28.24	08.24
3Q 2025 annual review: added step therapy bypass for IL HIM per IL HB 5395; for PHN, added member must use generic Gralise if available; in Appendix B, updated dosing regimens and clarified listed therapeutics alternatives have evidence supporting their use in the indications covered by this policy; references reviewed and updated.	05.06.25	08.25

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.