gabapentin ER (Gralise®); gabapentin enacarbil (Horizant®)
EOCCO POLICY

Policy Type: PA Pharmacy Coverage Policy: EOCCO197

Description
Gabapentin ER (Gralise) is an orally administered anticonvulsant. Gabapentin enacarbil (Horizant) is a prodrug of gabapentin.

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
gabapentin ER (Gralise)	300 mg tablets	Postherpetic neuralgia	60 tablets/30 days
	450 mg tablets		
	600 mg tablets		
	750 mg tablets		
	900 mg tablets		
	300 mg-600mg tablets Blister/Starter Pack		33 tablets (1 pack)/30 days
generic gabapentin ER	300 mg capsules	Postherpetic neuralgia	60 capsules/30 days
	600 mg capsules		
gabapentin enacarbil (Horizant)	300 mg tablets	Postherpetic neuralgia; Restless leg syndrome	30 tablets/30 days
	600 mg tablets		60 tablets/30 days

Initial Evaluation

I. **Gabapentin ER (Gralise) or gabapentin enacarbil (Horizant)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. A diagnosis of one of the following:
      1. **Postherpetic neuralgia (PHN); AND**
         i. Treatment with gabapentin, greater than or equal to, 1800 mg per day has been ineffective, contraindicated, or not tolerated; **AND**
         ii. Treatment with pregabalin has been ineffective, contraindicated, or not tolerated; **AND**

iii. If the request is for brand gabapentin ER (Gralise) 300mg or 600mg, treatment with generic gabapentin ER 300mg or 600mg has been ineffective, not tolerated, or contraindicated; **OR**
   a. Request is for 450mg, 750mg, 900mg, or 300mg-600mg starter pack; **OR**

2. **Moderate-to-severe primary restless leg syndrome**; **AND**
   i. Request is for gabapentin enacarbil (Horizant); **AND**
   ii. Treatment with **all** of the following has been ineffective, contraindicated, or not tolerated:
      a. pramipexole; **AND**
      b. ropinirole; **AND**
      c. pregabalin

II. Gabapentin ER (Gralise) and gabapentin enacarbil (Horizant) are considered investigational when used for all other conditions, including but not limited to:
   A. Diabetic peripheral neuropathy
   B. Postmastectomy pain syndrome
   C. Seizures
   D. Other neuropathic pain

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. A diagnosis of one of the following:
   A. Restless Leg Syndrome (RLS); **AND**
      1. Member has exhibited improvement or stability of restless leg syndrome symptoms [e.g., improved pain, sleep, fatigue]; **OR**
   B. Postherpetic neuralgia (PHN); **AND**
      1. Member has exhibited improvement or stability of symptoms [e.g. improved pain, skin sensitivity].

Supporting Evidence

I. Gabapentin ER (Gralise) and gabapentin enacarbil (Horizant) have not been adequately studied for safety and efficacy in pediatric patients under the age of 18 years.

II. A phase 3, placebo-controlled, randomized trial has shown gabapentin ER (Gralise) to be efficacious in decreasing pain associated with postherpetic neuralgia over placebo (p=0.013). Phase 4 studies have similarly suggested effectiveness in pain reduction in patients with postherpetic neuralgia.

III. A phase 3, placebo-controlled, randomized trial has shown gabapentin enacarbil (Horizant) to be efficacious in reducing pain associated with postherpetic neuralgia over placebo (p=0.013) after 13 weeks.

IV. Guidelines for postherpetic neuralgia recommend immediate release gabapentin as a first line treatment option. It is recommended patients trial gabapentin IR before switching to an extended-release gabapentin product such as gabapentin ER (Gralise) or gabapentin enacarbil (Horizant).

V. Standard of care for treatment of postherpetic neuralgia includes use of pregabalin as first line therapy.

VI. A phase 4, placebo-controlled randomized trial found gabapentin enacarbil (Horizant) to improve restless leg syndrome symptoms on patient reported scales (IRLS) over placebo (p=0.014) as well as clinician-assessed (CGI-I) scales (p=0.004) after 12 weeks of treatment.

VII. Restless leg syndrome guidelines, as published by the American Academy of Neurology (AAN), recommend dopamine agonists (e.g. pramipexole, ropinirole, rotigotine) and gabapentin enacarbil (Horizant) as first line treatment options. A small (n=39) double-blind, placebo-controlled trial investigated a possible reduced response to gabapentin enacarbil (Horizant) following long-term dopaminergic treatment. A significant difference (p=0.045) in restless leg syndrome symptoms (IRLS) was found between dopamine treatment-naïve and dopamine treatment-experienced individuals when treated with gabapentin enacarbil (Horizant). Patients who were dopamine-experienced had been treated with a dopamine agonist for at least 90% of the past 5 consecutive years. Although gabapentin enacarbil (Horizant) is recommend as a first-line therapy along with dopamine agonists, due to the small sample size, as well as the unknown effects of shorter-term uses of dopamine agonists on gabapentin enacarbil (Horizant) responses, enacarbil (Horizant) should not be chosen as a first-line agent over a dopamine agonist.

VIII. Restless leg syndrome guidelines as published by the American Academy of Neurology (AAN) also lists pregabalin as having moderate evidence for use in treatment of RLS aligned with ropinirole, a dopamine agonist.

Investigational or Not Medically Necessary Uses

I. Gabapentin ER (Gralise) and gabapentin enacarbil (Horizant) have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Diabetic peripheral neuropathy

i. A placebo-controlled, randomized trial found no significant difference in efficacy from placebo and three different doses of gabapentin enacarbil (Horizant) in subjects with diabetic peripheral neuropathy.

B. Postmastectomy pain syndrome
   i. A small (n=21) open-label study found a small positive improvement in pain intensity after 8 weeks with gabapentin ER (Gralise). Further placebo-controlled, randomized trials are needed to validate efficacy and safety for this indication.

C. Seizures
   i. Gabapentin ER (Gralise) and gabapentin enacarbil (Horizant) have not been adequately studied for efficacy and safety in the treatment of seizures.

D. Other neuropathic pain
   i. Gabapentin ER (Gralise) and gabapentin enacarbil (Horizant) have not been adequately studied for efficacy and safety in the treatment of neuropathic pain not associated with postherpetic neuralgia or restless leg syndrome.

References

1. Gralise [Prescribing Information]. Menlo Park, CA: Depomed. September 2012.
2. Horizant [Prescribing Information]. Research Triangle Park, NC: GSK. March 2013.
3. Gabapentin Enacarbil Adult Restless Leg Syndrome Post Marketing Commitment Study (CONCORD). *Clinicaltrials.gov.* 2014. (NCT 01668667)
4. Garcia-Borreguero D, et al. Reduced response to gabapentin enacarbil in restless legs syndrome following long-term dopaminergic treatment. Sleep Med. 2019 Mar;55:74-80. doi: 10.1016/j.sleep.2018.11.025.
5. Study of Safety and Effectiveness of GRALISE (Gabapentin) Tablets in the Treatment of Patients With Postherpetic Neuralgia in Clinical Practice. *Clinicaltrials.gov.* 2012 (NCT 01426230)
6. Belfer I, et al. Effect of gastroretentive gabapentin (Gralise) on postmastectomy pain syndrome: a proof-of-principle open-label study. Pain Rep. 2017 Apr 11;2(3):e596. doi: 10.1097/PR9.0000000000000596.
7. Rauck R, et al. A randomized, controlled trial of gabapentin enacarbil in subjects with neuropathic pain associated with diabetic peripheral neuropathy. Pain Pract. 2013 Jul;13(6):485-96. doi: 10.1111/papr.12014.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added new 300mg and 600mg gabapentin ER to the QL table; Added step through generic gabapentin ER before use of Gralise when using the 300mg or 600mg tablets/capsules	01/2024
Added new 450mg, 750mg, 900mg once-daily tab Gralise strengths to the QL table	05/2023
Update to new policy format, addition of pregabalin as required agent to try and fail, removal of renal status related criteria	10/2020
Previous review	11/2011