Clinical Policy: Pregabalin (Lyrica, Lyrica CR)

Reference Number: ERX.NPA.10
Effective Date: 06.01.15
Last Review Date: 05.22
Line of Business: Commercial, Medicaid

Revision Log

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

Description

Pregabalin (Lyrica®, Lyrica® CR), a structural derivative of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), is a calcium channel alpha 2-delta ligand with anti-nociceptive and anti-seizure effects.

FDA Approved Indication(s)

Lyrica is indicated for the treatment of:

- Neuropathic pain associated with diabetic peripheral neuropathy
- Postherpetic neuralgia
- Patients 1 month of age and older with partial onset seizures as adjunctive therapy
- Fibromyalgia
- Neuropathic pain associated with spinal cord injury

Lyrica CR is indicated for the treatment of:

- Neuropathic pain associated with diabetic peripheral neuropathy
- Postherpetic neuralgia

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

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Lyrica, Lyrica CR, pregabalin, and pregabalin CR are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Neuropathic Pain (must meet all)**:**

1. Diagnosis of neuropathic pain associated with diabetic neuropathy, postherpetic neuralgia, treatment of cancer (*immediate-release only*), or spinal cord injury;
2. Age ≥ 18 years;
3. Failure of a 30-day trial of gabapentin at ≥ 1,800 mg/day, unless contraindicated or clinically significant adverse effects are experienced;
4. Failure of a 30-day trial of a tricyclic antidepressant (TCA) (e.g., amitriptyline, nortriptyline, imipramine) at up to maximally indicated doses, unless clinically significant adverse effects are experienced, member's age is ≥ 65, or all are contraindicated;
5. Failure of a 30-day trial of a serotonin/norepinephrine reuptake inhibitor (SNRI) (e.g., duloxetine, venlafaxine) at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated;
6. If request is for controlled-release formulation, member must use immediate-release pregabalin, unless contraindicated or clinically significant adverse effects are experienced;
7. If request is for brand Lyrica, member must use generic pregabalin, unless contraindicated or clinically significant adverse effects are experienced;

8. Dose does not exceed one of the following (a, b, or c):
   a. Diabetic neuropathy: pregabalin – 300 mg per day; pregabalin CR – 330 mg per day;
   b. Neuropathic pain associated with treatment of cancer: pregabalin – 300 mg per day;
   c. Postherpetic neuralgia, neuropathic pain associated with spinal cord injury: pregabalin – 600 mg per day; pregabalin CR – 660 mg per day.

Approval duration: 12 months

B. Fibromyalgia (must meet all)**:**
1. Diagnosis of fibromyalgia;
2. Age ≥ 18 years;
3. Request is for immediate-release version;
4. If request is for brand Lyrica, member must use generic pregabalin, unless contraindicated or clinically significant adverse effects are experienced;
5. Failure of a 30-day trial of gabapentin at ≥ 1,800 mg/day, unless contraindicated or clinically significant adverse effects are experienced;
6. Failure of a 30-day trial of duloxetine at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
7. Failure of a 30-day trial of cyclobenzaprine or a TCA at up to maximally indicated doses, unless clinically significant adverse effects are experienced, member's age is ≥ 65, or all are contraindicated;
8. Dose does not exceed 450 mg per day.

Approval duration: 12 months

C. Partial Onset Seizures (must meet all)**:**
1. Diagnosis of partial onset seizures;
2. Prescribed by or in consultation with a neurologist;
3. Age ≥ 1 month;
4. Request is for immediate-release version;
5. Failure of gabapentin used as adjunctive therapy to other anticonvulsants, unless contraindicated or clinically significant adverse effects are experienced;
6. Failure of TWO anticonvulsants indicated for partial seizures (e.g., carbamazepine, phenytoin, valproic acid, oxcarbazepine, phenobarbital, lamotrigine, levetiracetam, topiramate, zonisamide, tiagabine, felbamate), unless clinically significant adverse effects are experienced or all are contraindicated;
7. If request is for brand Lyrica, member must use generic pregabalin, unless contraindicated or clinically significant adverse effects are experienced;
8. Pregabalin will be used as adjunctive therapy to other anticonvulsants;
9. Request meets one of the following (a or b):
   a. For members weighing < 30 kg: Dose does not exceed 420 mg per day.
   b. For members weighing ≥ 30 kg: Dose does not exceed 600 mg per day.

Approval duration: 12 months

D. Generalized Anxiety Disorder (off-label) (must meet all)**:**
1. Diagnosis of generalized anxiety disorder;
2. Age ≥ 18 years;
3. Request is for immediate-release version;
4. Failure of TWO of the following alternatives, unless clinically significant adverse effects are experienced or all are contraindicated: escitalopram, paroxetine, venlafaxine ER, duloxetine, buspirone;
5. If request is for brand Lyrica, member must use generic pregabalin, unless contraindicated or clinically significant adverse effects are experienced;
6. Dose does not exceed 600 mg per day.

Approval duration: 12 months

E. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
   b. Documentation supports that member is currently receiving Lyrica for partial onset seizures 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:
   a. Immediate-release pregabalin:
      i. Diabetic neuropathy, neuropathic pain associated with treatment of cancer: 300 mg per day;
      ii. Postherpetic neuralgia, partial-onset seizures, generalized anxiety disorder, and neuropathic pain associated with spinal cord injury: 600 mg per day;
      iii. For partial-onset seizures:
         a) For members weighing < 30 kg: 420 mg per day;
         b) For members weighing ≥ 30 kg: 600 mg per day;
      iv. Fibromyalgia: 450 mg per day;
   b. Controlled-release pregabalin:
      i. Diabetic peripheral neuropathy: 330 mg per day;
      ii. Postherpetic neuralgia, neuropathic pain associated with spinal cord injury: 660 mg per day.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:
- **A.** Dental pain;
- **B.** Essential tremor;
- **C.** Social phobia;
- **D.** 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 policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
SNRI: serotonin/norepinephrine reuptake inhibitor
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 and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
TCAs		
amitriptyline (Elavil®)	**Fibromyalgia**** 10 mg to 50 mg PO QD **Neuropathic**** 25 to 150 mg PO QHS	150 mg/day†
desipramine (Norpramin®)	**Diabetic Peripheral Neuropathy**** Initially 25 mg PO QHS, then titrate as tolerated to efficacy (usual range: 75 mg to 150 mg PO QHS) **Postherpetic Neuralgia**, Neuropathic Pain associated with Cancer Treatment **** 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†
imipramine (Tofranil®, Tofranil PM®)	**Diabetic Peripheral Neuropathy**** 50 mg to 150 mg PO QHS	150 mg/day
nortriptyline (Pamelor®)	**Diabetic Peripheral Neuropathy**** 50 mg to 75 mg PO daily **Postherpetic Neuralgia**** 75 mg to 150 mg PO daily **Neuropathic Pain associated with Cancer Treatment**** 50 to 150 mg PO QHS	150 mg/day
Serotonin/Norepinephrine Reuptake Inhibitors		
duloxetine (Cymbalta®)	**Fibromyalgia** 30 to 60 mg PO QD **Neuropathic pain**** 60 to 120 mg PO QD	120 mg/day
venlafaxine (extended-release) (Effexor XR®)	**Fibromyalgia**** 37.5 to 225 mg PO QD **Neuropathic pain**** 75 mg to 225 mg PO QD	225 mg/day
Miscellaneous		
gabapentin (immediate-release: Neurontin®; extended-release: Horizant®, Gralise®)	**Diabetic Peripheral Neuropathy**, Neuropathic Pain associated with Cancer Treatment**** *Immediate-release*: 300 mg PO TID titrated based on clinical response **Fibromyalgia**** 300 mg PO QHS then increased to target dosage of 2,400 mg/day **Postherpetic Neuralgia** *Immediate-release*: 300 mg PO QD on day 1, 300 mg PO BID on day 2, 300 mg PO TID on day 3, then titrate as needed to 1,800 mg/day *Extended-release (Gralise)*: 300 mg PO on day 1, 600 mg on day 2, 900 mg on days 3-6, 1,200 mg on	Immediate release: 3,600 mg/day† Gralise: 1,800 mg/day† Horizant: 1,200 mg/day†

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	days 7-10, 1,500 mg on days 11-14, and 1,800 mg on day 15 and thereafter *Extended-release (Horizant)*: 600 mg/day PO for 3 days, 600 mg PO BID on day 4 and thereafter **Partial Seizures** *Immediate-release*: Adults: initially 300 mg PO TID; effective range 900-1,800 mg/day but up to 2,400 mg/day has been used long term Children 3-12 years: 10-15 mg/kg/day PO in 3 divided doses; effective dose 25-35 mg/kg/day if > 5 years and 40 mg/kg/day if 3-4 years	
cyclobenzaprine (Flexeril®)	**Fibromyalgia**** 10 mg to 20 mg PO QHS	20 mg/day
Anticonvulsants		
carbamazepine (Carbatrol®, Epitol®, Equetro®, Tegretol®, Tegretol XR®)	Refer to prescribing information	Refer to prescribing information
felbamate (Felbatol®)		
levetiracetam (Elepsia XR®, Keppra®, Keppra XR®, Roweepra®, Spritam®)		
oxcarbazepine (Oxtellar XR®, Trileptal®)		
phenobarbital (Luminal®)		
phenytoin (Dilantin®, Phenytek®)		
tiagabine (Gabitril®)		
topiramate (Qudexy XR®, Topamax®, Topamax Sprinkle®, Topiragen®, Trokendi XR®)		
valproic acid (divalproex sodium, Depakote Sprinkle®, Depakote ER®, Depakote®, Depakene®)		
zonisamide (Zonegran®)		

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 use*
†Maximum dose for drug, not necessarily indication

Appendix C: Contraindications/Boxed Warnings
- Contraindication(s): known hypersensitivity to pregabalin or any of its components
- Boxed warning(s): none reported

Appendix D: General Information
- Class IIb recommendation in Micromedex for generalized anxiety disorder is supported by 5 randomized, double blind, placebo-controlled studies. It is also considered a second-line agent by the Canadian Psychiatric Association.

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
Pregabalin (Lyrica)*	Diabetic peripheral neuropathy	3 divided doses PO per day	300 mg/day
	Neuropathic pain associated with treatment of cancer	2 or 3 divided doses PO per day	300 mg/day
	Postherpetic neuralgia	2 or 3 divided doses PO per day	600 mg/day
	Partial onset seizures	Adults: 2 or 3 divided doses PO per day Pediatric patients weighing > 30 kg: 2.5 mg/kg/day in 2 or 3 divided doses Pediatric patients weighing < 30 kg: 3.5 mg/kg/day • 1 month to < 4 years old: 3 divided doses • ≥ 4 years old: 2 or 3 divided doses	Adults: 600 mg/day Pediatrics < 30 kg: 14 mg/kg/day
	Fibromyalgia	2 divided doses PO per day	450 mg/day
	Neuropathic pain associated with spinal cord injury	2 divided doses PO per day	600 mg/day
	Generalized anxiety disorder	Initially, 75 mg PO BID. If tolerated after 1 week, the dose may be increased to 150 mg PO BID. Thereafter, the dose may be adjusted according to response and tolerability. Data from clinical trials indicate an effective dose range is 150 to 225 mg PO BID.	600 mg/day
Pregabalin extended-release (Lyrica CR)	Diabetic peripheral neuropathy	165 mg PO QD. Dose may be increased to 330 mg PO QD within 1 week.	330 mg/day
	Postherpetic neuralgia	165 mg PO QD. Dose may be increased to 330 mg PO QD within 1 week. After 2 to 4 weeks of treatment, dose may be increased to 660 mg PO QD in patients not experiencing adequate pain relief.	660 mg/day

**Lyrica should be administered orally starting at 150 mg/day. It should be titrated up to 300 mg/day within 1 week for all indications except partial onset seizures.*

VI. Product Availability

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

VII. References

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Generalized Anxiety Disorder

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Cancer Treatment-related Neuropathic Pain
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Reviews, Revisions, and Approvals	Date	P&T Approval Date
2Q 2018 annual review: Neuropathic pain: modified criteria to require trial of TCA and SRNI; Fibromyalgia: modified criterion related to "failure of a 30 day trial of a TCA, cyclobenzaprine, or duloxetine" to require trial of duloxetine in addition to TCA or cyclobenzaprine since duloxetine is preferred/on formulary and FDA approved for fibromyalgia; Partial seizures: Modified requirement for failure of an anticonvulsant indicated for partial seizures to 2 anticonvulsants indicated for partial seizures; Added off-label indication: generalized anxiety disorder; Added dental pain, essential tremor, and social phobia as indications for which coverage is not authorized; References reviewed and updated.	01.25.18	05.18
2Q 2019 annual review: no significant changes; added Lyrica CR to policy; added Lyrica pediatric extension for partial onset seizure for those age ≥ 4 years (previously approved for age ≥ 12 years); added redirection to Lyrica for neuropathic pain; references reviewed and updated.	02.26.19	05.19
RT4: Added pediatric extension for the partial onset seizure for those ≥ 1 month, previously approved for ≥ 4 years; references reviewed and updated.	07.05.19	
Added redirection to generic pregabalin and medical justification why Brand Lyrica is requested in all criteria set; added Commercial and Medicaid line of business.	02.18.20	
2Q 2020 annual review: added off-label indication for neuropathy associated with treatment of cancer; allowed members 65 years old or older to bypass redirections to any TCA and cyclobenzaprine throughout the policy; references reviewed and updated.	02.19.20	05.20
2Q 2021 annual review: no significant changes; references reviewed and updated.	02.24.21	05.21
Added clarification that the policy applies to generic pregabalin, where applicable; clarified language for "Lyrica" to "pregabalin" where applicable to reduce confusion that policy also applies to generic pregabalin.	10.25.21	
2Q 2022 annual review: no significant changes; revised brand-to-generic redirection to "member must use" language; references reviewed and updated.	02.14.22	05.22

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.