Clinical Policy Title:	pregabalin
Policy Number:	RxA.411
Drug(s) Applied:	Lyrica®, Lyrica® CR
Original Policy Date:	03/06/2020
Last Review Date:	03/09/2021
Line of Business Policy Applies to:	All lines of business

Background

Pregabalin (Lyrica®), 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.

Lyrica® is indicated for the treatment of:

- Neuropathic pain associated with diabetic peripheral neuropathy
- Postherpetic neuralgia (PHN)
- 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 (PHN)

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
pregabalin (Lyrica®)	Diabetic peripheral neuropathy	3 divided doses orally per day	300 mg/day
pregabalin (Lyrica®)	Postherpetic neuralgia	2 or 3 divided doses orally per day	600 mg/day
pregabalin (Lyrica®)	Partial onset seizures	Adults: 2 or 3 divided doses orally 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	Adults: 600 mg/day Pediatrics < 30 kg: 14mg/kg/day

Dosing Information			
Drug Name	**Indication**	**Dosing Regimen**	**Maximum Dose**
		old: 3 divided doses • ≥ 4 years old: 2 or 3 divided doses	
pregabalin (Lyrica®)	Fibromyalgia	2 divided doses orally per day	450 mg/day
pregabalin (Lyrica®)	Neuropathic pain associated with spinal cord injury	2 divided doses orally per day	600 mg/day
pregabalin (Lyrica®)	Generalized anxiety disorder	Initially, 75 mg orally two times a day. If tolerated after 1 week, the dose may be increased to 150 mg orally three times a day. 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 orally two times a day.	600 mg/day
pregabalin extended-release (Lyrica® CR)	Diabetic peripheral neuropathy	165 mg orally once daily. Dose may be increased to 330 mg orally once daily within 1 week.	330 mg/day
pregabalin extended-release (Lyrica® CR)	Postherpetic neuralgia	165 mg orally once daily. Dose may be increased to 330 mg orally once daily within 1 week. After 2 to 4 weeks of treatment, dose may be increased to 660 mg orally once daily 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.*

Dosage Forms

- pregabalin (Lyrica®): Capsules: 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg
- pregabalin (Lyrica®): Oral solution: 20 mg/mL
- pregabalin extended-release (Lyrica® CR): Tablets: 82.5 mg, 165 mg, 330 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.

I. Initial Approval Criteria

A. Neuropathic Pain (must meet all):

1. Diagnosis of neuropathic pain associated with diabetic neuropathy, postherpetic neuralgia, 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 contraindicated or clinically significant adverse effects are experienced;
5. Failure of a 30-day trial of a formulary serotonin/norepinephrine reuptake inhibitor (SNRI) (e.g., duloxetine, venlafaxine) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
6. If Lyrica® CR is requested, medical justification supports inability to use pregabalin or Lyrica® (e.g., contraindications to excipients in Lyrica®);
7. Dose does not exceed:
   a. Diabetic neuropathy: Lyrica® – 300 mg per day; Lyrica® CR – 330 mg per day;
   b. Postherpetic neuralgia, neuropathic pain associated with spinal cord injury: Lyrica®– 600 mg per day; Lyrica® CR – 660 mg per day.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

B. 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 Lyrica®;
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 all are contraindicated or clinically significant adverse effects are experienced;
7. Lyrica® will be used as adjunctive therapy to other anticonvulsants;
8. Request meets one of the following (a or b):
   a. For patients weighing < 30 kg: dose does not exceed 14 mg/kg/day.
   b. For patients weighing ≥ 30 kg: dose does not exceed 600 mg per day.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

C. Fibromyalgia (must meet all):

1. Diagnosis of fibromyalgia;

2. Age ≥ 18 years;
3. Request is for Lyrica®;
4. Failure of a 30-day trial of gabapentin at ≥ 1,800 mg/day, unless contraindicated or clinically significant adverse effects are experienced;
5. Failure of a 30-day trial of duloxetine at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
6. Failure of a 30-day trial of cyclobenzaprine or a TCA at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
7. Dose does not exceed 450 mg per day.

Approval Duration
Commercial: 12 months
Medicaid: 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 Lyrica®;
4. Failure of TWO of the following alternatives, unless contraindicated or clinically significant adverse effects are experienced: escitalopram, paroxetine, venlafaxine ER, duloxetine, or buspirone;
5. Dose does not exceed 600 mg 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 meets one of the following (a or b):
   a. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
   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. Lyrica®:
      i. Diabetic peripheral neuropathy: 300 mg per day;
      ii. Postherpetic neuralgia, neuropathic pain associated with spinal cord injury, generalized anxiety disorder: 600 mg per day;
      iii. For partial-onset seizures:
         a. For patients weighing < 30 kg: dose does not exceed 425 mg per day.
         b. For patients weighing ≥ 30 kg: dose does not exceed 600 mg per day.
      iv. Fibromyalgia: 450 mg per day;
   b. Lyrica® CR:
      i. Diabetic peripheral neuropathy: 330 mg per day;
      ii. Postherpetic neuralgia, neuropathic pain associated with spinal cord injury: 660 mg per day.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key

FDA: Food and Drug Administration
SNRI: serotonin/norepinephrine reuptake inhibitor
TCA: tricyclic antidepressant

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
TCAs		
amitriptyline (Elavil®)	Diabetic Peripheral Neuropathy** 25 mg to 100 mg orally once daily Postherpetic Neuralgia** 25 mg to 137.5 mg (median: 75 mg) orally every day at bedtime Fibromyalgia** 10 mg to 50 mg orally once daily	150 mg/day†
desipramine (Norpramin®)	Diabetic Peripheral Neuropathy** Initially 25 mg orally every day at bedtime, then titrate as tolerated to efficacy (usual range: 75 mg to 150 mg orally every day at bedtime) Postherpetic Neuralgia** 10 to 25 mg orally every day at bedtime 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 orally every day at bedtime	150 mg/day
nortriptyline (Pamelor®)	Diabetic Peripheral Neuropathy** 50 mg to 75 mg orally daily Postherpetic Neuralgia** 75 mg to 150 mg orally daily	150 mg/day
Serotonin/Norepinephrine Reuptake Inhibitors		
duloxetine (Cymbalta®)	Diabetic Peripheral Neuropathy 60 mg orally once daily Fibromyalgia 30 to 60 mg orally once daily	60 mg/day
venlafaxine extended- release (Effexor XR®)	Diabetic Peripheral Neuropathy** 75 mg to 225 mg orally once daily Fibromyalgia** 37.5 to 150 mg orally once daily	225 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Miscellaneous		
gabapentin (immediate- release: Neurontin®; extended-release: Horizant®, Gralise®)	Diabetic Peripheral Neuropathy** *Immediate-release*: 300 mg orally three times a day titrated based on clinical response Fibromyalgia** 300 mg orally every day at bedtime then increased to target dosage of 2400 mg/day Postherpetic Neuralgia *Immediate-release*: 300 mg orally once daily on day 1, 300 mg orally two times a day on day 2, 300 mg orally three times a day on day 3, then titrate as needed to 1800 mg/day *Extended-release (Gralise)*: 300 mg PO on day 1, 600 mg on day 2, 900 mg on days 3-6, 1200 mg on days 7-10, 1500 mg on days 11-14, and 1800 mg on day 15 and thereafter *Extended-release (Horizant)*: 600 mg/day orally for 3 days, 600 mg orally two times a day on day 4 and thereafter Partial Seizures *Immediate-release*: • Adults: initially 300 mg orally three times a day; effective range 900-1800 mg/day but up to 2400 mg/day has been used long term • Children 3-12 years: 10-15 mg/kg/day orally in 3 divided doses; effective dose 25-35 mg/kg/day if > 5 years and 40 mg/kg/day if 3-4 years	Immediate release: 3600 mg/day† Gralise®: 1800 mg/day† Horizant®: 1200 mg/day†
cyclobenzaprine (Flexeril®)	Fibromyalgia** 10 mg to 20 mg orally every day at bedtime	20 mg/day
Anticonvulsants		
carbamazepine (Carbatrol®, Epitol®, Equetro®, Tegretol®, Tegretol XR®)	Initial, 200 mg orally twice daily for the first week; may increase by adding up to 200 mg/day in 2 divided doses at weekly intervals to the optimal response.	1200 mg/day
felbamate (Felbatol®)	Partial seizures Monotherapy/Adjunctive therapy: 1200 mg/day orally in 3 to 4 divided doses.	3600 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
lamotrigine (Lamictal®, Lamictal CD®, Lamictal ODT®, Lamictal XR®)	Partial onset seizures and generalized onset seizures Lamictal® ODT 25 mg every Other Day to 500 mg once daily, in divided doses Lamictal® XR: 25 mg every other day to 600 mg oraly once daily.	500 mg/day 600 mg/day
levetiracetam (Elepsia XR®, Keppra®, Keppra XR®, Roweepra®, Spritam®)	Partial onset seizures and generalized onset seizures *Immediate-release tablet, injection, oral solution, or tablet for oral suspension*: Initial, 500 mg twice daily IV/orally; titration, may increase by increments of 1000 mg/day every 2 weeks in 2 divided doses. *Extended-release tablet*: Initial, 1000 mg orally once daily; titration, may increase by increments of 1000 mg/day every 2 weeks.	3000 mg/day
oxcarbazepine (Oxtellar XR®, Trileptal®)	Partial seizures *Extended-release tablet:* Initial 600 mg/day orally once daily for 1 week on an empty stomach; may increase in 600 mg/day increments at weekly intervals to 1200 to 2400 mg/day *Immediate-release tablet or suspension:* Initial, 300 mg orally twice a day; may increase weekly by up to 600 mg/day	2400 mg/day 1200 mg/day
phenobarbital (Luminal®)	Seizures 60 to 200 mg/day or 50 to 100 mg 2 to 3 times daily	400 mg/day
phenytoin (Dilantin®, Phenytek®)	Partial onset seizures and generalized onset seizures Initial dose: 1 g divided into 3 doses Maintenance dose: 100 mg orally 3 to 4 times a day	300 mg/day 600 mg/day
tiagabine (Gabitril®)	Partial seizures (Adjunct) *Patients taking enzyme-inducing antiepileptic drugs:* Initial - 4 mg orally once daily Maintenance - 32 to 56 mg/day *Patients not receiving enzyme-inducing AED regimens:* 12 mg/day	56 mg/day
topiramate (Qudexy XR®, Topamax®, Topamax Sprinkle®, Topiragen®, Trokendi XR®)	Seizures Initial dose 25 to 50 mg orally once daily; maintenance dose of 200 to 400 mg/day	400 mg/day
valproic acid (divalproex sodium, Depakote Sprinkle®, Depakote ER®, Depakote®, Depakene®)	Partial onset seizures and generalized onset seizures Initial dose of 10 to 15 mg/kg/day orally (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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
zonisamide (Zonegran®)	Partial seizures (adjunct) Initial dose 100 mg/day orally; may increase dosage by 100 mg/day every 2 weeks to the usual effective dosage range of 100 to 600 mg/day in 1 to 2 divided doses	400 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 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

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.

References

1. Lyrica Prescribing Information. New York, NY: Pfizer Inc.; June 2020. Available at: http://labeling.pfizer.com/showlabeling.aspx?id=561 Accessed February 08, 2021.
2. Lyrica CR Prescribing Information. New York, NY: Pfizer Inc.; June 2020. Available at: http://labeling.pfizer.com/ShowLabeling.aspx?id=9678 Accessed February 08, 2021.
3. O'Connor AB, Dworkin RH. Treatment of neuropathic pain: an overview of recent guidelines. Am J Med. 2009; 122(10): S22-S32.
4. Pop-Busui R, Boulton A, Feldman E, et al. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. Diabetes Care Jan 2017, 40 (1) 136-154.
5. Bril V, England J, Franklin GM, et al. Evidence-based guideline: treatment of painful diabetic neuropathy, a report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology. 2011; 76(20): 1758-1765.
6. Bouilton AJM, Vinik AI, Arezzo JC, et al. Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care. 2005; 28(4): 956-962.
7. 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 (reaffirmed in 2008). Neurology. 2004; 63(6): 969- 965.
8. Clauw DJ. Fibromyalgia: a clinical review. JAMA. 2014; 311(15): 1547-1555.
9. Glauser T, Ben-Menachem E, Bourgeois B, et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia. 2013; 54(3): 551-563.
10. Brodie MJ. Pregabalin as adjunctive therapy for partial seizures. Epilepsia. 2004; 45(S6): 19- 27.
11. Rickels K, Pollack MH, Feltner DE, Et Al: Pregabalin For Treatment Of Generalized Anxiety Disorder: A 4-Week,

Multicenter, Double-Blind, Placebo-Controlled Trial Of Pregabalin And Alprazolam. Arch Gen Psychiatry. 2005; 62(9):1022-1030.
12. Montgomery SA; Tobias K; Zornberg GL; Kasper S; Pande AC. Efficacy And Safety Of Pregabalin In The Treatment Of Generalized Anxiety Disorder: A 6-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Comparison Of Pregabalin And Venlafaxine. J Clin Psychiatry. 2006:67: 771-782.
13. Pohl RB; Feltner DE; Fieve RR; Pande AC. Efficacy Of Pregabalin In The Treatment Of Generalized Anxiety Disorder: Double-Blind, Placebo-Controlled Comparison Of Bid Versus Tid Dosing. J Clin Psychopharmacol. 2005;25:151-158.
14. Pande AC, et al. Pregabalin in generalized anxiety disorder: a placebo-controlled trial. Am J Psychiatry. 2003;160:533-540.
15. Canadian Psychiatric Association. Clinical practice guidelines management of anxiety disorders: Generalized Anxiety Disorder. Can J Psychiatry. 2006;51(suppl2):51S-55S.
16. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2018. Available at: http://www.clinicalpharmacology-ip.com/. Accessed February 08, 2021.
17. DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed February 08, 2021.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/2020	03/06/2020
Updated References	4/30/2020	5/20/2020
Policy was reviewed: 1. Clinical policy was updated. 2. Line of business was updated to all line of business. 3. HIM was removed from Initial and continued therapy criteria approval duration. 4. Commercial approval duration was updated for initial and continued therapy criteria. 5. Continued therapy II.A.1 was rephrased to “Member is currently receiving medication that has been authorized by RxAdvance..”. 6. PO, QHS, BID, TID was updated to orally, every day at bed time, two times a day and three times a day respectively throughout the policy. 7. In Appendix B: dosing regimen for anticonvulsants drugs was updated. 8. References were reviewed and updated.	02/08/2021	03/09/2021