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Medication Policy Manual

Policy No: dru122

Topic: Lyrica®, pregabalin

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IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Pregabalin (Lyrica®) is a medication used to treat seizures and specific types of pain. It is classified as an anticonvulsant medication. Pregabalin is a controlled substance (Schedule V).

Policy/Criteria

- I.** Most contracts require prior authorization approval of pregabalin prior to coverage. Pregabalin may be considered medically necessary for the following conditions when all of the associated criteria are met:
- A.** Seizures.
- OR**
- B.** Neuropathic pain when a previous history of adequate treatment courses of at least 30 days with each of the following medications are ineffective, unless contraindicated or not tolerated:
 - 1.** Gabapentin (Neurontin®)
- AND**
- 2.** At least one generic medication listed in *Appendix 1*.
- OR**
- C.** Fibromyalgia when a previous history of adequate treatment courses of at least 30 days with each of the following medications are ineffective, unless contraindicated or not tolerated:
 - 1.** Gabapentin (Neurontin®).
- AND**
- 2.** At least one generic medication listed in *Appendix 1*.
- II.** Administration, Quantity Limitations, and Authorization Period
- A.** Regence Pharmacy Services considers pregabalin to be a self-administered medication.
 - B.** When prior authorization is approved, pregabalin may be authorized in quantities of up to three capsules per day, not exceeding 600 mg per day.
 - C.** Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.
- III.** Pregabalin is considered not medically necessary when used for the following conditions:
- A.** Generalized anxiety disorder.
 - B.** Social anxiety disorder.
- IV.** Pregabalin is considered investigational when used for all other conditions, including, but not limited to:
- A.** Alcohol withdrawal.
 - B.** Chronic daily headache.
 - C.** Essential tremor.
 - D.** Hot flashes.

- E. Migraine headache.
- F. Restless legs syndrome (RLS).
- G. Chronic prostatitis/chronic pelvic pain syndrome.
- H. Post-Operative pain relief

Position Statement

- Pregabalin is a seizure medication approved for the treatment of partial onset seizures, neuropathic pain associated with diabetes, neuropathic pain resulting from spinal cord injury, postherpetic neuralgia, and fibromyalgia.
- There are several proven, preferred/formulary medication options available to treat all of the conditions listed above.
- Pregabalin has not been shown to be better than any of these other formulary options.
- Pregabalin is chemically similar to gabapentin (Neurontin®).
- Pregabalin has significant side effects and has not been shown to be better tolerated than other medication options.
- Pregabalin is a schedule V controlled substance because its use may lead to physical dependence and abuse.

Summary

- There are many other treatment options (including gabapentin) available for management of the conditions where pregabalin might be used.

Adjunctive treatment in Partial seizures

- * carbamazepine (Tegretol®) (used alone or in combination) [1]
- * phenytoin (Dilantin®) (used alone or in combination) [1]
- * lamotrigine (Lamictal®) [2]
- * oxcarbazepine (Trileptal®) [3]
- * topiramate (Topamax®) [4]
- * gabapentin [7]
- * zonisamide (Zonegran®) [6]
- * levetiracetam (Keppra®) [7]
- * tiagabine (Gabitril®) [8]

Pain Associated with Diabetic Neuropathy

- * tricyclic antidepressants [10]
- * antiepileptic drugs (gabapentin, carbamazepine, phenytoin) [9-11]

Pain Associated with Postherpetic Neuralgia

- * gabapentin, tricyclic antidepressants, opioids, tramadol [12-15]

Fibromyalgia

- * amitriptyline, cyclobenzaprine, gabapentin [16, 40]

Generalized Anxiety Disorder

- * antidepressants such as amitriptyline, imipramine, venlafaxine, fluoxetine, citalopram, sertraline and paroxetine [17, 38]
- * benzodiazepines such as alprazolam, lorazepam [33, 38]
- * buspirone [38, 39]
- The current level of evidence for pregabalin, as well as other traditional alternatives, does not allow for conclusions that one option provides additional clinical benefit over another.

Clinical Efficacy

TREATMENT OF PARTIAL ONSET SEIZURES

- Like other newer anti-epileptic drugs (AEDs), studies with pregabalin are limited to use primarily as adjunctive therapy in the treatment of partial seizures.
- As add-on therapy, pregabalin in doses of 150mg to 600mg per day over 12 weeks provided statistically significant reductions in the frequency of partial seizures. [19-21, 36]
- The percent of patients who achieved greater than or equal to 50% reduction in seizure frequency with pregabalin over 12 weeks was statistically significant over placebo. [19-21]
 - * \approx 14-31% with 150mg/day (NNT ranging from 3 to 7).
 - * \approx 40% with 300mg/day (NNT ranging from 2 to 3).
 - * \approx 43-51% with 600mg/day (NNT ranging from 2 to 3).
- The efficacy of adjunctive pregabalin has been compared to adjunctive levetiracetam therapy in a randomized noninferiority trial. Results from this study indicate that pregabalin is noninferior and has similar tolerability to levetiracetam as adjunctive therapy in reducing seizure frequency in patients with partial seizures. [64]
- Two short-term studies evaluated pregabalin compared to lamotrigine and gabapentin as monotherapy for treatment of partial seizures. Pregabalin did not demonstrate superior safety or efficacy when compared to lamotrigine or gabapentin. [58]

NEUROPATHIC PAIN ASSOCIATED WITH DIABETIC PERIPHERAL NEUROPATHY, POSTHERPETIC NEURALGIA OR PAIN DUE TO SPINAL CORD INJURY

- Pregabalin has been evaluated in at least four clinical trials (n=1067) for the treatment of diabetic peripheral neuropathy (DPN) [22-25] and in two studies (n=411) for the treatment of postherpetic neuralgia (PHN). [26-27]
- These trials provide uncertain evidence about the efficacy of pregabalin for these conditions.
- The trials reported that treatment with pregabalin over 5-12 weeks was associated with reductions in patient-reported pain scores compared to treatment with placebo. [22-25]

- Some of these trials used pregabalin doses higher than recommended for DPN [22-24] and PHN. [26]
- * DPN: Pregabalin has been studied in doses up to 600mg/day for DPN; however, there is no evidence that this dose confers additional benefit over the labeled dose (for DPN) of 300mg/day. [18]
- * PHN: The recommended dose for pregabalin in PHN is up to 300mg/day. Doses of pregabalin up to 600mg/day (in divided doses) are reserved for patients who have ongoing pain and are tolerating 300mg/day. [18]
- All of the trials of pregabalin in PHN and DPN excluded individuals with a previous failure on gabapentin 1200mg/day and therefore pre-selected patients who may have a more favorable response to pregabalin. [22-25]
- Additionally, PHN trials with pregabalin were confounded by allowing concomitant analgesic medications (such as narcotic and non-narcotic analgesics, nonsteroidal anti-inflammatory drugs, aspirin and antidepressants during the study). [26-27, 37]
- Tricyclic antidepressant medications and gabapentin are effective options for the treatment of DPN and PHN. [9-11, 14] There is no evidence that pregabalin is more effective than either of these options.
- Carbamazepine is the gold standard for treatment of trigeminal neuralgia. [44]

FIBROMYALGIA

- The studies that evaluated pregabalin in fibromyalgia compared it to placebo. [28, 41-42, 50-52] There is no information that shows how well pregabalin works relative to established therapies such as amitriptyline, cyclobenzaprine, or gabapentin.
- FDA approval of pregabalin for fibromyalgia was based on two randomized, placebo-controlled trials. [41-42, 50-51]
 - * Efficacy was evaluated based on reduction in mean pain score (11-point Likert scale) or time to loss of therapeutic response, defined as less than 30% reduction in pain score or worsening of fibromyalgia symptoms.
 - * Approximately 49% of subjects receiving pregabalin 450mg/day achieved a 30% reduction in pain versus 30% in the placebo group.
 - In other words, five to six patients must be treated for 14 weeks for one patient to achieve at least a 30% reduction in pain from baseline.
 - * A 50% improvement in pain was achieved in 27% of subjects receiving pregabalin versus 15% of subjects in the placebo group. [41]
 - In other words, eight to nine patients must be treated for 14 weeks for one patient to achieve at least a 50% reduction in pain from baseline.
 - * Of the subjects reporting at least a 50% reduction in pain score with pregabalin in a 6-week open label run-in, 62% had a loss of therapeutic response after 26 weeks of therapy versus 81% on placebo. [42]

- In a third trial that studied the efficacy of pregabalin in fibromyalgia, the magnitude of benefit reported for the primary efficacy endpoint (a mean pain score difference of -0.93 points between pregabalin versus placebo and based on daily diary ratings using an 11-point pain intensity scale of 0 = no pain and 10 = worst pain) was of uncertain clinical significance. [28]
 - * Flaws in the design of this study included concomitant use of analgesic medications (confounding variables) and pre-selection of subjects which may have favored the pregabalin treatment group (the trial excluded subjects with a previous failure on gabapentin 1,200 mg per day).
- Overall, pregabalin may provide a modest benefit for some patients with fibromyalgia pain; however, this benefit may wane after weeks to months of therapy.

Efficacy of other medications in fibromyalgia pain

- The unlabeled use of the following therapies is supported by randomized controlled trials and several guidelines on the management of fibromyalgia (Goldenberg DL, et al. *JAMA* 2004; Buckhardt CS, et al. American Pain Society 2005): [16, 40, 45]
 - * Medications: amitriptyline, cyclobenzaprine, and gabapentin.
 - * Non-medication therapies: aerobic exercise, muscle strengthening, patient education, and cognitive-behavioral therapy.
- Similar to pregabalin, these medications (amitriptyline, cyclobenzaprine, and gabapentin) provide modest benefit to some patients with fibromyalgia pain.
- A study funded by the National Institutes of Health found that **gabapentin** (Neurontin) given in doses of 1,200 mg/day to 2,400 mg/day over 12 weeks decreased pain in patients with fibromyalgia better than placebo. [40]
 - * The study was of similar design and reported similar results as the pregabalin trials.
 - * Pain severity was self-reported based on a pain intensity scale ranging from 0 to 10 (0 = no pain, and 10 = worst pain imaginable).
 - * A 30% reduction in pain was achieved in 51% of subjects who received gabapentin and in 30% of subjects who received placebo. In other words, five patients must be treated for 12 weeks for one patient to achieve a 30% reduction in pain from baseline.

ALCOHOL WITHDRAWAL

- A small (n=37 per group), single-blind, randomized trial suggests that pregabalin was modestly better than lorazepam in the treatment of alcohol withdrawal syndrome as assessed by the number of patients alcohol free at the end of the study. [53]
- An additional small (n=42), randomized-controlled trial suggests that when compared to placebo, pregabalin did not demonstrate efficacy in the treatment of alcohol withdrawal syndrome. Larger, well-controlled trials are necessary to support the benefit of pregabalin in this population. [59]

CHRONIC DAILY HEADACHE

- There are no published clinical trials that support the use of pregabalin in the treatment of chronic daily headache.

ESSENTIAL TREMOR

- There is a small (n = 22) randomized controlled trial (RCT) that studied pregabalin in patients with essential tremor. [48] Larger, well-controlled trials are necessary to support the benefit of pregabalin in this population.

GENERALIZED ANXIETY/SOCIAL ANXIETY DISORDERS

- There are many medications from several different classes of medications which are widely used to treat anxiety symptoms. These options include antidepressants (SSRIs, tricyclic antidepressants, monoamine oxidase inhibitors, and venlafaxine), benzodiazepines (e.g., lorazepam, alprazolam), and buspirone. [38]
- Medication is used to get anxiety symptoms under control while other interventions, such as cognitive-behavioral therapy, are initiated. [38]
- Several studies have also evaluated pregabalin in treating symptoms of anxiety. [29-32, 34-35, 60] There is no reliable information that pregabalin is more effective than these other options.
 - * Pregabalin was compared with lorazepam [29, 30], alprazolam [34], or venlafaxine [35] in the treatment of generalized anxiety disorder. The studies had flaws that included a high number of patients that did not complete the trials, and use of other medications that could lead to misinterpretation of the results (confounders).
- Pregabalin has not been shown to be safer or better tolerated than established treatment options for treating anxiety.

HOT FLASHES

- A randomized, double-blind, placebo-controlled trial compared the efficacy of pregabalin to placebo in reducing the frequency of hot flashes in 207 adult women with “bothersome” hot flashes. At the end of six weeks, pregabalin 75 mg twice daily and 150 mg twice daily reduced the frequency of hot flashes by 15% and 21%, respectively, compared to placebo (p = 0.009 and p=0.007). However, an excessive number of subjects (21%) were excluded in the final analysis, rendering the results of this trial as not useful.[54]

MIGRAINE HEADACHE

- There are no published clinical trials that support the use of pregabalin in the treatment of migraine headache.

RESTLESS LEG SYNDROME (RLS)

- Two small, randomized, placebo-controlled trials have been published evaluating pregabalin in the treatment of patients with restless leg syndrome. These trials both suggested a modest, but statistically significant improvement in International Restless Legs Score (IRLS). However, the trials were small and suffered from high patient attrition, and are of uncertain usefulness. Larger, well-controlled trials are necessary to support the benefit of pregabalin in this population. [55,56]
- There is a single, small (< 20 subjects), uncontrolled observational trial that studied pregabalin in restless leg syndrome in patients with or without neuropathic pain. [43] Larger, well-controlled trials are necessary to support the benefit of pregabalin in this population.

CHRONIC PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME

- One systematic review has been published evaluating pregabalin for treatment of chronic prostatitis/chronic pelvic pain syndrome. The review suggests that pregabalin does not improve symptoms. The amount of available evidence is small and larger well-controlled trials are necessary to support the benefit of pregabalin in this population. [61]

POST-OPERATIVE PAIN RELIEF

- Two small, randomized-controlled trials have been published evaluating pregabalin in the treatment of Post-Operative pain relief.
- The trials are inconclusive regarding the benefit of adding pregabalin for Post-Operative pain relief in patients following surgery. Larger, well-controlled trials are necessary to support the benefit of pregabalin in this population. [62-63]

Safety

- There are currently no studies that allow for a direct comparison of the safety of pregabalin with other treatment options.
- The most common adverse effects observed with pregabalin are: [18]

	pregabalin vs. placebo	NNH
- dizziness	21-38% vs. 5-9%	3 to 6
- somnolence	12-22% vs. 3-5%	5 to 11
- weight gain	1-2% vs. 4-12%	10 to 33
- peripheral edema	2-4% vs. 5-12%	12 to 33
- blurred vision	1-3% vs. 5-10%	14 to 25
- abnormal thinking	0-2% vs. 2-8%	16 to 50
- dry mouth	1-3% vs. 4-8%	20 to 33

- Similar to pregabalin, these are also the most commonly reported adverse events observed with gabapentin and tricyclic antidepressants.
- Adverse effects were dose-related, with higher doses being associated with a higher incidence of adverse effects.

- Across individual clinical trials, typical discontinuation rates due to adverse events for pregabalin (dose range 300 to 600mg/day) ranged from approximately 7 to 30%, versus approximately 3 to 8% for placebo.
- Pregabalin is rated as a Schedule V controlled substance because it has the potential to cause a similar “high” as benzodiazepines (e.g., diazepam) and its use may lead to physical dependence. ^[18]

Dosing and Administration

- Recommended dosing for pregabalin: ^[18]
 - * Partial onset seizures: 150 mg to 600 mg per day, divided into two or three doses.
 - * Neuropathic pain associated with DPN: 150 mg to 300 mg per day, divided in two or three doses.
 - * Postherpetic neuralgia: 300 mg to 600 mg per day, divided in two or three doses.
 - * Fibromyalgia: 300 to 450 mg per day, divided in two doses.
 - * Neuropathic pain associated with spinal cord injury: 300 mg to 600 mg per day, divided in two doses.
- Dosing with pregabalin should begin at 75 mg twice daily or 50 mg three times daily in order to minimize adverse events and improve tolerability. ^[18]
- Pregabalin is available as a capsule in 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg dosage strengths. ^[18]
- Because pregabalin is eliminated primarily by renal excretion, package labeling recommends dose reduction in renal failure. ^[18]
- When discontinuing pregabalin, a gradual taper over a minimum of one week is recommended to prevent potential of withdrawal symptoms. ^[18]

Appendix 1: Generic Alternatives to pregabalin.	
Neuropathic pain:	Amitriptyline (Elavil) Desipramine (Norpramin) Duloxetine (Cymbalta) Imipramine (Tofranil) Nortriptyline (Pamelor)
Fibromyalgia:	Amitriptyline (Elavil) Cyclobenzaprine (Flexeril) Desipramine (Norpramin) Duloxetine (Cymbalta) Imipramine (Tofranil) Nortriptyline (Pamelor)

Cross References
High-cost Antidepressant Medications, Medication Policy Manual, Policy No. 352

Codes	Number	Description
N/A		

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Revision History

Revision Date	Revision Summary
5/13/2016	No criteria changes