

## PHARMACY / MEDICAL POLICY – 5.01.521

# Pharmacologic Treatment of Neuropathy, Fibromyalgia, and Seizure Disorders


Effective Date: Mar. 1, 2025  
Last Revised: Feb. 24, 2025  
Replaces: N/A

### RELATED POLICIES / GUIDELINES:

5.01.520 Antidepressants: Pharmacy Medical Necessity Criteria for Brands  
5.01.529 Management of Opioid Therapy  
5.01.550 Pharmacotherapy of Arthropathies  
5.01.605 Medical Necessity Criteria for Pharmacy Edits

Select a hyperlink below to be directed to that section.

[POLICY CRITERIA](#) | [DOCUMENTATION REQUIREMENTS](#) | [CODING](#)  
[RELATED INFORMATION](#) | [EVIDENCE REVIEW](#) | [REFERENCES](#) | [HISTORY](#)

 Clicking this icon returns you to the hyperlinks menu above.

## Introduction

Neuropathy is a term that refers to problems with one or more nerves. Neuropathy doesn't always cause symptoms, but usually it does. Depending on the location of the nerve and the type of damage, symptoms can include loss of feeling, numbness, tingling, or pain. Neuropathic nerve pain has been described as feeling like an electric shock, burning, or knifing. Extreme sensitivity to touch may be another symptom. Fibromyalgia is a long-term medical condition that often causes pain in muscles and bones, areas that are tender to the touch, and fatigue. It's believed that fibromyalgia is the result of changes in how the brain and spinal cord process pain signals from the nerves. Seizure disorders are the result of unusual electrical activity in the brain. Uncontrolled electrical signals in the brain produce several symptoms, including seizures. This policy describes specific medications that may be approved for neuropathy, fibromyalgia, and seizure disorders.

**Note:** The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

## Policy Coverage Criteria

Documentation in the form of chart notes/medical records must be provided with prior authorization review for the agents described below.

Drug	Medical Necessity
<p><b>Lyrica (pregabalin)</b></p> <p><b>Managed under pharmacy benefit</b></p>	<p><b>Lyrica (pregabalin) may be considered medically necessary for the treatment of neuropathic pain when all the following are met:</b></p> <ul style="list-style-type: none"> <li>• The individual is aged 18 years or older</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Has tried and had an inadequate response or intolerance to generic gabapentin</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Has tried and had an inadequate response or intolerance to ONE of the following generic medications:             <ul style="list-style-type: none"> <li>○ A tricyclic antidepressant (e.g., amitriptyline)</li> <li>○ An SNRI (e.g., duloxetine, venlafaxine)</li> </ul> </li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Has tried and had an inadequate response or intolerance to generic pregabalin or generic pregabalin extended-release</li> </ul> <p><b>Lyrica (pregabalin) may be considered medically necessary for the treatment of a seizure disorder when all the following are met:</b></p> <ul style="list-style-type: none"> <li>• The individual is aged 1 month or older</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• Has tried and had an inadequate response or intolerance to generic pregabalin or generic pregabalin extended-release</li> </ul> <p><b>Lyrica (pregabalin) may be considered medically necessary for the treatment of fibromyalgia when all the following are met:</b></p> <ul style="list-style-type: none"> <li>• The individual is aged 18 years or older</li> </ul> <p><b>AND</b></p>

Drug	Medical Necessity
	<ul style="list-style-type: none"> <li>Has tried and had an inadequate response or intolerance to generic gabapentin</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Has tried and had an inadequate response or intolerance to TWO of the following generic medications:               <ul style="list-style-type: none"> <li>A tricyclic antidepressant (e.g., amitriptyline)</li> <li>An SNRI (e.g., duloxetine, venlafaxine)</li> <li>Cyclobenzaprine</li> <li>Tramadol</li> </ul> </li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Has tried and had an inadequate response or intolerance to generic pregabalin or generic pregabalin extended-release</li> </ul> <p><b>Lyrica (pregabalin) may be considered medically necessary for the treatment of generalized anxiety disorder when all the following are met:</b></p> <ul style="list-style-type: none"> <li>The individual is aged 18 years or older</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Has tried and had an inadequate response or intolerance to a generic SSRI (e.g., citalopram, fluoxetine)</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Has tried and had an inadequate response or intolerance to ONE of the following generic medications:               <ul style="list-style-type: none"> <li>Benzodiazepines (e.g., alprazolam, clonazepam)</li> <li>Buspirone</li> <li>Venlafaxine</li> <li>Hydroxyzine</li> <li>Duloxetine</li> </ul> </li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Has tried and had an inadequate response or intolerance to generic pregabalin or generic pregabalin extended-release</li> </ul>
<p><b>Lyrica CR (pregabalin extended-release)</b></p> <p><b>Managed under pharmacy benefit</b></p>	<p><b>Lyrica CR (pregabalin extended-release) may be considered medically necessary for the treatment of diabetic peripheral neuropathy or postherpetic neuralgia when all the following are met:</b></p> <ul style="list-style-type: none"> <li>The individual is aged 18 years or older</li> </ul>



Drug	Medical Necessity
	<p><b>AND</b></p> <ul style="list-style-type: none"> <li>Has tried and had an inadequate response or intolerance to generic gabapentin</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Has tried and had an inadequate response or intolerance to ONE of the following generic medications:             <ul style="list-style-type: none"> <li>A tricyclic antidepressant (e.g., amitriptyline)</li> <li>An SNRI (e.g., duloxetine, venlafaxine, desvenlafaxine)</li> </ul> </li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Has tried and had an inadequate response or intolerance to generic pregabalin or generic pregabalin extended-release</li> </ul>
<p><b>Qutenza (capsaicin)</b></p> <p><b>Managed under medical benefit</b></p>	<p><b>Qutenza (capsaicin) may be considered medically necessary for the treatment of diabetic peripheral neuropathy or postherpetic neuralgia when all the following are met:</b></p> <ul style="list-style-type: none"> <li>The individual is aged 18 years or older</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Has tried and had an inadequate response or intolerance to generic gabapentin</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Has tried and had an inadequate response or intolerance to ONE of the following generic medications:             <ul style="list-style-type: none"> <li>A tricyclic antidepressant (e.g., amitriptyline)</li> <li>An SNRI (e.g., duloxetine, venlafaxine, desvenlafaxine)</li> </ul> </li> </ul>
<p><b>Savella (milnacipran)</b></p> <p><b>Managed under pharmacy benefit</b></p>	<p><b>Savella (milnacipran) may be considered medically necessary for the treatment of fibromyalgia when all the following are met:</b></p> <ul style="list-style-type: none"> <li>The individual is aged 18 years or older</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Has tried and had an inadequate response or intolerance to generic gabapentin</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Has tried and had an inadequate response or intolerance to TWO of the following generic medications:             <ul style="list-style-type: none"> <li>A tricyclic antidepressant (e.g., amitriptyline)</li> <li>An SNRI (e.g., duloxetine, venlafaxine)</li> <li>Cyclobenzaprine</li> <li>Tramadol</li> </ul> </li> </ul>

Drug	Not Medically Necessary
<ul style="list-style-type: none"> <li>• Lyrica (pregabalin)</li> <li>• Lyrica CR (pregabalin extended-release)</li> <li>• Qutenza (capsaicin)</li> <li>• Savella (milnacipran)</li> </ul>	All other uses of Lyrica (pregabalin), Lyrica CR (pregabalin extended-release), Qutenza (capsaicin), and Savella (milnacipran) for conditions not outlined in this policy are considered not medically necessary.

Drug	Investigational
<ul style="list-style-type: none"> <li>• Lyrica (pregabalin)</li> <li>• Lyrica CR (pregabalin extended-release)</li> <li>• Qutenza (capsaicin)</li> <li>• Savella (milnacipran)</li> </ul>	Lyrica (pregabalin), Lyrica CR (pregabalin extended-release), Qutenza (capsaicin), and Savella (milnacipran) are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.

Length of Approval	
Approval	Criteria
Initial authorization	Non-formulary exception reviews and all other reviews for drugs listed in this policy may be approved up to 12 months.
Re-authorization criteria	Non-formulary exception reviews and all other reviews for drugs listed in this policy may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.

Documentation Requirements
<p>The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:</p> <ul style="list-style-type: none"> <li>• Office visit notes that contain the diagnosis, relevant history, physical evaluation and medication history</li> </ul>

## Coding

Code	Description
<b>HCPCS</b>	
J7336	Capsaicin 8% patch (Qutenza), per sq cm

## Related Information

### Benefit Application

Qutenza (capsaicin) is managed through the medical benefit. All other drugs in this policy are managed through the pharmacy benefit.

### Consideration of Age

The ages stated in this policy for which Lyrica (pregabalin), Lyrica CR (pregabalin extended-release), Qutenza (capsaicin), or Savella (milnacipran) are considered medically necessary are based on the ages approved in the FDA prescribing information.

## Evidence Review

### Description

#### Pathophysiology and Disease Burden of Neuropathy

Neuropathy is a general term for pain or other sensory disturbance resulting from a lesion or dysfunction in the nervous system. Neuropathic pain may be associated with abnormal sensations (dysesthesia) which occur without external stimuli and allodynia, abnormal sensations occurring in response to stimuli. Neuropathic pain may be continuous or episodic. Individuals often describe neuropathic pain in terms of familiar sensations such as electric shock, burning or knifing pain. Sensations of coldness, "pins and needles", numbness and itching may also be present, and allodynia may result from normal stimuli, such as bedclothes touching or rubbing the individual's skin.

A general population-based survey in the U.K. published in 2006 estimated neuropathic pain prevalence to be 8%. Neuropathic pain may result from disorders of the peripheral nervous system or the central nervous system and is common in such conditions as stroke, spinal cord injury, multiple sclerosis, diabetes, HIV and cancer, where it may be caused by the tumor compressing nerves, by pathologic fractures in individuals with bone metastases or by many of the cytotoxic chemotherapeutic agents employed in cancer treatment. Neuropathic pain may be peripheral or central in origin, and it may be nociceptive (direct result of physical trauma) or nonnociceptive. Diabetic and post-herpetic neuropathy were covered in previous reviews.

## **Pharmacology of Duloxetine**

Duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake. Duloxetine has no significant affinity for dopaminergic, adrenergic, cholinergic, histaminergic, opioid, glutamate, and GABA receptors in vitro. Although the exact mechanisms of the antidepressant and central pain inhibitor action of duloxetine are unknown, they are believed to be related to the drug's potentiation of serotonergic and noradrenergic activity in the CNS.

Evidence suggests that pain reduction in response to duloxetine is independent of its antidepressant effect and can be demonstrated even in non-depressed individuals. Analysis suggests that 50-90% of the observed effect is independent of antidepressant activity.

## **Rationale**

### **Therapeutic Alternatives**

Prior to the approval of duloxetine and pregabalin, individuals with neuropathies were treated with a number of unapproved different medications. While some other agents have shown efficacy in controlled clinical trials the treatment of this condition has frequently been seen as unsatisfactory. One guideline exists for the treatment of neuropathic pain, but it was created prior to the introduction of duloxetine and pregabalin. The neuropathic pain guideline was drafted by members of the faculty of the Fourth International Conference on the Mechanisms and Treatment of Neuropathic Pain. Five first-line medications (gabapentin, the 5% lidocaine patch opioid analgesics, tramadol hydrochloride, and TCAs) are recommended on the basis that their efficacy have been consistently demonstrated in randomized controlled trials.



## **Tricyclic Antidepressants**

These drugs, most specifically amitriptyline and imipramine, are serotonin and norepinephrine reuptake inhibitors (SNRI). They were the first class of drugs proven to be effective in neuropathic pain. The doses used in neuropathic pain are lower than those used for depression. They are usually initiated at 10 to 25 mg at night then titrated up every 3 to 7 days as tolerated. This class of drugs significant adverse effects has limited their usefulness in many individuals. Amitriptyline is the most studied agent in this class, but efficacy seems to correlate with the SNRI profile, found mostly in the tertiary amine compounds.

## **Gabapentin**

Gabapentin, an amino acid structurally related to GABA, has been shown in clinical trials to significantly reduce neuropathic pain compared to placebo. Doses up to 3600mg/day were used with long titration phases of up to 3-8 weeks. Some of the studies also demonstrated improvements in sleep, mood, and quality of life scores. The mechanism of gabapentin in analgesia is not fully understood.

## **5% Lidocaine Patch**

Lidocaine patch is a topical anesthetic that works by preventing the generation and conduction of nerve impulses. It is FDA approved for the treatment of post herpetic neuralgia and efficacy for this indication was demonstrated in two published placebo-controlled trials. Individuals in these studies obtained significantly greater pain relief from the lidocaine patch compared to a vehicle only placebo patch. The patches are dosed as no more than three patches on at a time for no more than 12 hours out of the day. The patch is also limited to individuals whose lesions can be covered by three patches.

## **Opioid Analgesics**

Long-acting oxycodone, an opioid agonist, has been studied in both PHN and DPN. In PHN, individuals on oxycodone CR up to 60mg/day had a significant reduction in pain, disability, and allodynia compared to individuals in the placebo group. DPN individuals on oxycodone CR up to 120mg/day obtained significantly reduced pain, improvement of daily activities and sleep. However, the value of this class of drugs in neuropathic pain individuals is limited by the risk of opioid dependence.





## **Tramadol**

Tramadol, a serotonin and norepinephrine reuptake inhibitor with a  $\mu$  opioid agonist metabolite, has been shown in two trials to be effective in the treatment of DPN. In these two trials, doses up to a maximum of 400mg/day significantly reduced pain compared to placebo.

Combination therapy is generally more effective than a single agent. Anecdotally, combining an NSAID, an opioid and a pain blocking agent (antidepressant, AED, lidocaine, etc.) seems to be the most effective strategy. When patients do not have a satisfactory response to treatment with the five first-line medications alone or in combination, several medications may be considered for second-line use. Recommendations for second-line medications are based on positive results from a single randomized controlled trial or inconsistent results from multiple randomized controlled trials. Other medications sometimes used for the treatment of neuropathic pain patients include capsaicin, clonidine, dextromethorphan, and mexiletine. Non-drug therapies (i.e., massage, physical therapy, acupuncture, etc.) are also frequently employed for neuropathic pain, as well as several other alternative medicine approaches.

The extent to which non-allopathic treatments for neuropathy are resorted to is indicative of the failure of allopathic approaches to adequately manage this all-too-common problem. Neuropathy patients are often frustrated and can easily become dependent on opioid medications. A combination of two or three drugs is often the best pharmacologic way to manage these patients. Unfortunately, the appropriate combination must be empirically determined, often after repeated trial of alternatives. Referral of these patients to a multidisciplinary pain clinic may be necessary.

## **Cymbalta (duloxetine)**

Two short-term (12 week) Phase III, pivotal, placebo-controlled trials, and one 52-week, open-label, parallel group extension safety study provided the evidence for FDA approval for diabetic peripheral neuropathy. These unpublished studies consistently indicate that short-term, acute use of duloxetine, at doses of 60-120 mg QD, significantly decreases 24-hour average pain score, and increases the proportion of "responders" (defined as a  $\geq 30\%$  reduction in baseline pain severity) compared with placebo. While a dose of 120 mg/day was shown to be safe and effective, there is no evidence that doses  $> 60$  mg/day confer additional significant benefit, and the higher dose is less well tolerated.



For fibromyalgia, there are currently no head-to-head trials being conducted to compare duloxetine against any of the other agents recommended for treatment of FM. The three published trials comparing duloxetine versus placebo in treating FM resulted in conclusive evidence of duloxetine's efficacy in treating FM, albeit the treatment phase for all three trials were relatively short (12 weeks, 12 weeks, and 6 months). Duloxetine, dosed at 60mg to 120mg/d, was shown to be efficacious at significantly reducing painful symptoms of FM, as well as the amount of tender points and interference with various aspects of daily life. Data from two of the 3 trials suggested better efficacy and improved outcomes are seen in women versus men.

### **Savella (milnacipran)**

Milnacipran is an SNRI approved for fibromyalgia. Efficacy studies show milnacipran is more effective than placebo at 3 months for fibromyalgia; however, data at 6 months appears less consistent. No comparative trials with other agents for fibromyalgia are available. Elevated blood pressure, heart rate and LFTs appear to be of concern with milnacipran and use of this agent is not recommended in patients with liver dysfunction, substantial alcohol use, or uncontrolled blood pressure or heart rate.

### **Lyrica (pregabalin)**

Pregabalin has demonstrated modest efficacy in placebo-controlled trials in neuropathic pain individuals. No head-to-head comparison studies with other drugs have been reported. The level of evidence of effectiveness in treating neuropathic pain is greatest for tricyclic antidepressants with mixed serotonin and norepinephrine reuptake inhibition (SNRIs) such as amitriptyline. Pregabalin may be of benefit to a subset of complex partial seizure individuals who are refractory to standard first line therapies and is approved to treat fibromyalgia.

Pregabalin is more effective than placebo for symptomatic relief of associated pain and management of symptoms associated with fibromyalgia. Individuals were considered responders if they had at least a 30% decrease in pain on the Pain Visual Analog Scale (VAS). The greatest relief of pain and symptoms was seen at a dose of 450mg/day. There was no evidence of greater effect of pain scores for the 600mg daily dose than the 450mg daily dose.

Three studies examining the efficacy have been conducted. Subjects taking pregabalin had a higher percentage of people with a 30% reduction in pain and had overall improvement of symptoms compared to placebo. These results aren't all that clinically relevant. At best, the proportion of subjects experiencing at least a 30% reduction in pain score was 50% for



pregabalin vs. 30% for placebo. The data show that pregabalin is statistically better than placebo, but not much better. In many cases, relevant data have been omitted, e.g., baseline mean values of the endpoints that would indicate the magnitude of actual improvement with pregabalin.

A 2016 randomized, double-blind, placebo-controlled study evaluated 107 adolescents (12 – 17 years) with fibromyalgia who received pregabalin or placebo. Improvement in the primary endpoint, change from baseline in mean pain score at 15 weeks, was not statistically significant between pregabalin and placebo, with a treatment difference -0.66 (95% CI -1.51 – 0.18; P=0.121). Of all individuals with adverse events (AEs) there were 70.4% in the pregabalin arm and 64.% in the placebo arm. The study noted a post hoc analysis demonstrated there were significant differences in response between subjects from the US and those from other countries, but no explanation was provided. The most common adverse events with pregabalin were dizziness (29.6%) and nausea (22.2%), with 13.2% and 9.4% in the placebo arm. A 6-month open-label extension study with a total of 63 subjects were evaluated from the original study for additional safety information. 71.4% of individuals experienced one or more adverse events. The most commonly reported adverse events were dizziness (22.2%), fatigue (12.7%), headache (9.5%), and nausea/abdominal pain/upper abdominal pain (7.9%).

### **Qutenza (capsaicin)**

The efficacy of Qutenza was established in two 12-week, double-blind, randomized, dose-controlled, multicenter clinical trials. These studies enrolled individuals with postherpetic neuralgia (PHN) persisting for at least 6 months following healing of herpes zoster rash and a baseline score of 3-9 on an 11-point Numerical Pain Rating Scale (NPRS) ranging from 0 (no pain) to 10 (worst possible pain). Qutenza and a control topical system were each applied as a single, 60-minute application. The control used in these studies looked similar to Qutenza but contained a low concentration of the active ingredient, capsaicin (3.2 mcg/cm<sup>2</sup> , 0.04% w/w), to retain blinding regarding the known application site reactions of capsaicin (such as burning and erythema). The baseline mean pain score across the 2 studies was approximately 6.0. Individuals who entered the study on stable doses of pain-control medications were required to keep the dosing stable throughout the duration of the study. Approximately half of the individuals were taking concomitant medications, including anticonvulsants, non-SSRI antidepressants, or opioids for their PHN at study entry. Prior to application, a topical anesthetic was applied to the treatment area for 60 minutes. Individuals were permitted to use local cooling and additional analgesic medications for treatment-related discomfort as needed through Day 5. Individuals recorded their pain daily in a diary.



PHN Study 1: In this 12-week study, the Qutenza group demonstrated a greater reduction in pain compared to the control group during the primary assessment at Week 8. The percent change in average pain from baseline to Week 8 was -18% ( $\pm 2\%$ ) for the low-dose control and -29% ( $\pm 2\%$ ) for Qutenza. PHN Study 2: In this 12-week study, the Qutenza group demonstrated a greater reduction in pain compared to the control group during the primary assessment at Week 8. The percent change in average pain from baseline to Week 8 was -26% ( $\pm 2\%$ ) for the low-dose control and -33% ( $\pm 2\%$ ) for Qutenza.

## 2010 Update

A recent update of the NICE guidelines for drug treatment of neuropathic pain as well as a review newly published in the US (Dworkin, et al.) recommend amitriptyline and gabapentin as first line agents. The importance of evaluating psychosocial factors and use of cognitive behavioral therapy in management was discussed in a recent review by Turk, et al. These and other systematic reviews and expert recommendations continue to support this policy.

## 2011 Update

Policy updated to incorporate newly FDA-approved indication for Cymbalta in chronic musculoskeletal pain. No other significant updates to the literature were found.

## 2012 Update

No information was revealed that would prompt a change in policy.

## 2014 Update

Policy updated to include generic SNRI trial as a qualifier for coverage.

## 2015 Update

Policy updated with the addition of duloxetine as a qualifier for Generalized Anxiety Disorder.



## 2016 Update

A literature search was conducted between June 1, 2015, and December 6, 2016. No new information was found that would prompt a change to the existing policy criteria.

## 2017 Update

A literature search was conducted between July 1, 2016, and November 2, 2017. No new information was found that would prompt a change to the existing policy criteria.

## 2018 Update

A literature search was conducted between November 1, 2017, and October 2, 2018. An updated Cochrane meta-analysis of SNRI use in fibromyalgia reported that evidence quality for this therapy continues to be “low to very low”. Another Cochrane review found little evidence for combination therapy involving drugs from several classes. Evidence also does not support the use of cannabidiol. No new information was found that would indicate the need for a change to the existing policy criteria.

## 2019 Update

Reviewed Lyrica (pregabalin), Lyrica CR (pregabalin extended-release) and Savella (milnacipran) prescribing information and conducted a literature search from August 1, 2018, through August 20, 2019. Updated coverage criteria based on the ages approved in the FDA labeling. Added buspirone as a qualifying medication for the treatment of generalized anxiety disorder for Lyrica (pregabalin).

## 2020 Update

Reviewed Lyrica (pregabalin), Lyrica CR (pregabalin extended-release) and Savella (milnacipran) prescribing information. No new information was identified that would result in a change to the policy coverage criteria.



## 2021 Update

Reviewed Lyrica (pregabalin), Lyrica CR (pregabalin extended-release) and Savella (milnacipran) prescribing information. No new information was identified in prescribing information that would result in a change to the policy coverage criteria. Added generic pregabalin extended-release to policy and updated coverage criteria for Lyrica and Lyrica CR to require use of generic pregabalin or generic pregabalin extended-release first.

## 2022 Update

Reviewed Lyrica (pregabalin), Lyrica CR (pregabalin extended-release) and Savella (milnacipran) prescribing information and conducted a literature search on the management of fibromyalgia. No new information was identified that would result in a change to the policy coverage criteria. Removed generic pregabalin and generic pregabalin extended-release from policy as prior authorization was removed for these two generic drugs.

## 2023 Update

Reviewed prescribing information of all the drugs in this policy. No new information was identified that would result in a change to the policy coverage criteria. Changed "patient" to "individual" for the process of standardization.

## 2024 Update

Reviewed prescribing information of all the drugs in this policy. The following policy changes are effective July 4, 2024: added coverage criteria for Qutenza (capsaicin) for the treatment of postherpetic neuralgia and diabetic peripheral neuropathy. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.



## 2025 Update

Reviewed prescribing information of all the drugs in this policy. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months.

## References

1. Crofford L, Rowbotham MC, Mease PJ, Russell IJ, Dworkin RH, Corbin AE, Young Jr. JP, LaMoreaux LK, Martin SA, Sharma U. Pregabalin 1008-105. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* 2005; 52(4):1264-73.
2. Lyrica (pregabalin) package insert. Pfizer Inc, New York, NY. Revised December 2023.
3. The National Institute of Diabetes and Digestive and Kidney Diseases (2002) Diabetic Neuropathies: The Nerve Damage of Diabetes. NIH Publication No. 02-3185.
4. Duby J, Campbell R, Setter S, White J, Rasmussen K. Diabetic neuropathy: an intensive review. *Am J Health Syst Pharm.* 2004;61:103-173.
5. Sumner CJ, Sheth S, Griffin JW, Cornblath DR, Polydefkis M. The spectrum of neuropathy in diabetes and impaired glucose tolerance. *Neurology.* 2003;60:108-111.
6. Schmader KE. Epidemiology and impact on quality of life of post-herpetic neuralgia and painful diabetic neuropathy. *Clin J Pain.* 2002;18:350-354.
7. Backonja MM, Serra S. Pharmacologic management part 1: better-studied neuropathic pain diseases. *Pain Medicine.* 2004;5:S28-S47.
8. Dworkin RH, Backonja MM, Rowbotham MC, Allen RR, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. *Arch Neurol.* 2003;60:1524-1534.
9. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum* 1995; 38: 19-28.
10. Chakrabarty S, Zoorob R. Fibromyalgia. *Am Fam Physician* 2007;76:247-54.
11. Berger A, Dukes E, Martin S, Edelsberg J, Oster G. Characteristics and healthcare costs of patients with fibromyalgia syndrome. *Int J Clin Pract* 2007; 61:1498-1508.
12. White LA, Birnbaum HG, Kaltenboeck A, Tang J, Mallett D, Robinson RL. Employees with fibromyalgia: medical comorbidity, healthcare costs, and work loss. *J Occup Environ Med.* 2008; 50: 13-24.
13. Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. *JAMA* 2004; 292: 2388-2395.
14. Goldenberg DL. Pharmacological treatment of fibromyalgia and other chronic musculoskeletal pain. *Best Practice and Research Clinical Rheumatology* 2007; 21:499-511.
15. Cymbalta (duloxetine hydrochloride) delayed-release capsules prescribing information. Eli Lilly and Company; Indianapolis, IN. Revised August 2023.
16. Mease PJ, Clauw DJ, Gendreau M, et al. The efficacy and safety of milnacipran for treatment of fibromyalgia. A randomized, double blind, placebo controlled trial. *J Rheumatol* 2009;36:398-409.



17. Clauw DJ, Mease P, Palmer RH, Gendreau RM and Wang Y. Milnacipran for the treatment of fibromyalgia in adults: a 15 week, multicenter, randomized, double blind, placebo controlled, multiple dose clinical trial. *Clin Ther* 2008;30(11):1988-2004.
18. Clauw DJ, Palmer RH, Thacker K, et al. Milnacipran efficacy in the treatment of fibromyalgia syndrome: a 15-week, randomized, double blind, placebo-controlled trial. Poster presented at the American College of Rheumatology Annual Scientific Meeting, Boston, Massachusetts, November 6-11, 2007.
19. Gendreau RM, Thorn MD, Gendreau JF, et al. Efficacy of milnacipran in patients with fibromyalgia. *J Rheumatol* 2005;32:1975-1985.
20. Tan T, et al.; Guideline Development Group, Pharmacological management of neuropathic pain in non-specialist settings: summary of NICE guidance. *BMJ* 2010;340:c1079.
21. Turk DC, Audette J, Levy RM, et al. Assessment and treatment of psychosocial comorbidities in patients with neuropathic pain. *Mayo Clin Proc.* 2010 Mar;85(3 Suppl):S42-50.
22. Dworkin RH, O'Connor AB, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin Proc.* 2010 Mar;85(3 Suppl):S3-14.
23. Malemud CJ. Focus on pain mechanisms and pharmacotherapy in the treatment of fibromyalgia syndrome. *Clin Exp Rheumatol.* 2009 Sep-Oct;27(5 Suppl 56):S86-91.
24. Arnold LM, Schikler KN, Bateman L, et al. Safety and efficacy of pregabalin in adolescents with fibromyalgia: a randomized, double-blind, placebo-controlled trial and a 6-month open-label extension study. *Pediatr Rheumatol Online J.* 2016;14:46.
25. Lyrica CR (pregabalin extended release) package insert. Pfizer Inc, New York, NY. Revised December 2023.
26. Savella (milnacipran) package insert. Allergan USA, Inc, Irvine, CA. Revised May 2024.
27. Welsch P, Üçeyler N, Klose P, et al. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia. *Cochrane Database Syst Rev.* 2018 Feb 28;2:CD010292.
28. Thorpe J, Shum B, Moore RA, Combination pharmacotherapy for the treatment of fibromyalgia in adults. *Cochrane Database Syst Rev.* 2018 Feb 19;2:CD010585.
29. Qutenza (capsaicin) packaging insert. Averitas Pharma. Morristown, NJ. Revised July 2024.

## History

Date	Comments
12/13/05	Add to Prescription Drug Section - New Policy—effective January 1, 2006.
08/08/06	Replace Policy - Policy reviewed with literature search by Pharmacy and Therapeutic Committee on July 25, 2006. Policy statement updated with exenatide and thiazolidinediones added as medically necessary; Policy Guidelines and Rationale sections updated; references added.
05/08/07	Replace Policy - Policy statement for exenatide updated with additional criteria; Policy Guidelines updated to reflect addition to policy statement. Reviewed by P&T on March 27, 2007.
06/12/07	Replace Policy - Policy statement on coverage criteria for exenatide (Byetta), sitagliptin and esomeprazole (Nexium) expanded; medically necessary indications for 5HT3





Date	Comments
	antagonists, Actiq and Fentora added to policy statement. Policy Guidelines updated and Rationale updated; references added
12/11/07	Replace Policy - Policy reviewed with literature search by Pharmacy and Therapeutic Committee on May 15, 2007. Policy statement updated to include Pregabalin as either medically necessary or investigational under the criteria. Acyclovir, famciclovir and valacyclovir as medically necessary under criteria. References added.
04/08/08	Replace Policy - Policy updated with literature search by Pharmacy. Policy statement was updated to include fibromyalgia as a medically necessary indication under Pregabalin. References added.
12/16/08	Replace Policy - Policy updated with literature search by Pharmacy. Policy statement updated to include the use of leukotriene modifiers for the treatment of allergic rhinitis refractory to nasal corticosteroids under the medically necessary indication.
02/10/09	NEW PR Policy PR.5.01.521 - Policy updated with literature search by Pharmacy. New PR policy. Medically Necessary and Investigational statements added. Policy split from PR.5.01.605
07/14/09	Replace Policy - Policy updated with literature search by Pharmacy. Policy statement updated to include milnacipran (Savella) for the treatment of fibromyalgia under the medically necessary indication. References added.
08/11/09	Minor update to Policy Guidelines section - Added "agents" after pharmacologic for all 3 drugs in the policy guidelines section.
09/15/09	Minor updates - Corrected spelling errors, no other changes.
06/08/10	Minor update to Policy guidelines section - Policy updated with literature search. Removed ": may be approved after a three month trial" from the policy guidelines for each drug. Added references.
05/10/11	Replace Policy - Policy updated with literature review; newly FDA-approved indication for Cymbalta in chronic musculoskeletal pain added to policy statements. No other changes.
06/26/12	Replace policy. Policy updated with literature review; no change in policy statements.
11/13/12	Replace policy. Policy Guidelines section updated with updated to the labeling on Lyrica, which now includes patients with post-herpetic neuropathy or neuropathic pain resulting from spinal cord injury.
11/26/12	Update Related Policies. Add 5.01.529.
02/11/13	Replace policy. Minor update to policy statement for duloxetine; clarification added to the medically necessary labeled indication for chronic musculoskeletal pain due to chronic osteoarthritis pain and chronic low back pain (previously this stated "including" versus "due to"). The Policy Guidelines were updated to align with this change.



Date	Comments
07/08/13	Minor Update – Clarification was added to the policy that it is managed through the member's pharmacy benefit; this is now listed in the header and within the coding section.
12/06/13	Update Related Policies. Change title for 5.01.520.
03/17/14	Replace policy. Policy updated to include generic SNRI trial as a qualifier for coverage.
04/14/14	Interim update. Policy updated with the addition of pregabalin (Lyrica) as medically necessary for the treatment of Generalized Anxiety Disorder when there have been trials and failure of at least two standard anxiolytic medications. Related policy 5.01.601 replaced with 5.01.550.
09/08/14	Interim update. Policy updated within the Policy Guidelines section only: indication for Pregabalin (Lyrica) changed to patients with neuropathic pain, with reference of root cause of the neuropathy or neuropathic pain removed, when criteria are met.
03/20/15	Update Related Policies. Change title to 5.01.550.
07/14/15	Annual Review. Added duloxetine as a qualifier for Generalized Anxiety Disorder.
01/01/17	Annual Review, approved December 13, 2016. No new information was found that would prompt a change to the existing policy criteria. Minor grammatical corrections were made to the reference section.
12/01/17	Annual Review, approved November 21, 2017. Clarified criteria for Lyrica. Added a reference.
03/01/18	Interim Review, approved February 27, 2018. Added criteria for Lyrica CR and revised duplicative content in Savella and Lyrica criteria sections. Dosage guide for Lyrica was removed.
07/01/18	Interim Review, approved June 5, 2018. Added requirement of documentation in the form of chart notes/medical records for medical necessity review of medications within this policy.
11/01/18	Annual Review, approved October 26, 2018. Annual review completed. No changes to policy criteria.
10/01/19	Annual Review, approved September 5, 2019. Updated coverage criteria for Lyrica and Savella. Added generic pregabalin to policy.
02/01/20	Interim Review, approved January 9, 2020. Updated coverage criteria for Lyrica and Lyrica CR to require use of generic pregabalin first.
10/01/20	Annual Review, approved September 1, 2020. No changes to policy statements.
07/01/21	Annual Review, approved June 22, 2021. Updated coverage criteria for Lyrica and Lyrica CR to require use of generic pregabalin or generic pregabalin extended-release first. Added generic pregabalin extended-release to policy.



Date	Comments
07/01/22	Annual Review, approved June 27, 2022. Removed generic pregabalin and generic pregabalin extended-release from policy as prior authorization was removed for these two generic drugs.
06/01/23	Annual Review, approved May 22, 2023. Reviewed prescribing information of all the drugs in this policy. No new information was identified that would result in a change to the policy coverage criteria. Changed "patient" to "individual" for the process of standardization.
04/01/24	Annual Review, approved March 12, 2024. The following policy changes are effective July 4, 2024, following 90-day provider notification. Added coverage criteria for Qutenza (capsaicin) for the treatment of postherpetic neuralgia and diabetic peripheral neuropathy. Added HCPCS code J7336.
01/01/25	Interim Review, approved December 10, 2024. Updated coverage criteria for all medications in this policy to specify that the prerequisite medication tried is a generic dosage form. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information.
03/01/25	Annual Review, approved February 24, 2025. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months.

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2025 Premiera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

