Pharmacologic Treatment of Neuropathy, Fibromyalgia and Seizure Disorders

**Number**: 5.01.521*

**Effective Date**: January 1, 2017

**Revision Date(s)**: 12/13/16; 07/14/15; 09/08/14; 04/14/14; 03/10/14; 02/11/13; 11/13/12; 06/12/12; 05/10/11; 06/8/10; 7/14/09; 2/10/09

**Replaces**: N/A

*This policy is managed through the Pharmacy benefit.

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**Policy**

*Milnacipran (Savella™)* may be considered medically necessary for the labeled indication of fibromyalgia. (See **Policy Guidelines**)

Use of *milnacipran (Savella™)* for other indications is considered investigational.

*Pregabalin (Lyrica®)* may be considered medically necessary neuropathic pain, fibromyalgia or refractory partial seizures. (See **Policy Guidelines**)

*Pregabalin (Lyrica®)* may be considered medically necessary for the treatment of Generalized Anxiety Disorder when there have been trials and failure of at least two standard anxiolytic medications*, at least one of which was an SSRI. (See **Policy Guidelines**)

*SSRI, venlafaxine, benzodiazepines, hydroxyzine

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**Related Policies**

- **5.01.520**  Antidepressants: Pharmacy Medical Necessity Criteria for Brands
- **5.01.529**  Opioid Analgesics
- **5.01.550**  Pharmacotherapy of Arthropathies
- **5.01.605**  Medical Necessity Criteria for Pharmacy Edits

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**Policy Guidelines**

*Milnacipran (Savella™)* may be covered in the following circumstances:

- Patients with fibromyalgia when they have failed a reasonable combination of pharmacologic agents,
including gabapentin and at least 2 of the following:
  o A tricyclic antidepressant (e.g., amitriptyline); and/or
  o A generic SNRI (e.g. duloxetine, venlafaxine); and/or
  o Cyclobenzaprine; and/or
  o Tramadol.

Pregabalin (Lyrica®) may be covered under the following circumstances:
- Patients with neuropathic pain who have failed trials of gabapentin AND a tricyclic antidepressant (e.g., amitriptyline) or a generic SNRI (e.g., duloxetine, venlafaxine, desvenlafaxine), unless it is contraindicated
- Patients with a seizure disorder will be considered on an individual case basis
- Patients with fibromyalgia when they have failed a reasonable combination of pharmacologic agents, including gabapentin AND at least 2 of the following:
  o A tricyclic antidepressant (e.g., amitriptyline); and/or
  o A generic SNRI (e.g. duloxetine, venlafaxine); and/or
  o Cyclobenzaprine; and/or
  o Tramadol.
- Patients with Generalized Anxiety Disorder after a trial and failure of an SSRI (e.g., citalopram, fluoxetine) plus one of the following:
  o Benzodiazepines (e.g., alprazolam, clonazepam)
  o Venlafaxine
  o Hydroxyzine
  o Duloxetine

Approved quantities of pregabalin should be limited to the maximum dose of 600mg per day in diabetic peripheral neuropathy, post-herpetic neuropathy and fibromyalgia patients. This limit does not apply to seizure patients.

### 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 alldynia, abnormal sensations occurring in response to stimuli. Neuropathic pain may be continuous or episodic. Patients 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 alldynia may result from normal stimuli, such as bedclothes touching or rubbing the patient’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 cause by the tumor compressing nerves, by pathologic fractures in patients 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 patients. Analysis suggests that 50-90% of the observed effect is independent of antidepressant activity.

This policy applies to the following medications:
- Pregabalin (Lyrica®)
- Milnacipran (Savella™)

**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 services representative to determine whether there are any benefit limitations applicable to this service or supply. This policy does not apply to Medicare Advantage.

**Benefit Application**

Applies to all pharmacy benefit contracts that include Pharmacy Prior Authorization Edits.

**Rationale**

**Therapeutic Alternatives**

Prior to the approval of duloxetine and pregabalin, patients 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 patients. 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. Patients 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 patients 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, patients on oxycodone CR up to 60mg/day had a significant reduction in pain, disability, and allodynia compared to patients in the placebo group. DPN patients 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 patients is limited by the risk of opioid dependence.

**Tramadol**

Tramadol, a serotonin and norepinephrine reuptake inhibitor with a µ 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 a number of other alternative medicine approaches.

The extent to which non-allopathic treatments for neuropathy are resorted is indicative of the failure of allopathic approaches to adequately manage this all too common problem. Neuropathy patients are often frustrating 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.

**Duloxetine (Cymbalta)**

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 ≥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 three trials suggested better efficacy and improved outcomes are seen in women versus men.

**Milnacipran (Savella™)**

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.

**Pregabalin (Lyrica®)**
Pregabalin has demonstrated modest efficacy in placebo-controlled trials in neuropathic pain patients. 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 patients 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. Patients 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.

**2010 Update**
A recent update of the NICE guidelines for drug treatment of neuropathic pain as well as a review newly published in the U.S. (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**
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.
References


3. Data on file – Lilly Pharmaceuticals, Indianapolis, IN.


# History

<table>
<thead>
<tr>
<th>Date</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/13/05</td>
<td>Add to Prescription Drug Section - New Policy—effective January 1, 2006.</td>
</tr>
<tr>
<td>08/08/06</td>
<td>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.</td>
</tr>
<tr>
<td>05/08/07</td>
<td>Replace Policy - Policy statement for exenatide updated with additional criteria; Policy Guidelines updated to reflect addition to policy statement. Reviewed by P&amp;T on March 27, 2007.</td>
</tr>
<tr>
<td>06/12/07</td>
<td>Replace Policy - Policy statement on coverage criteria for exenatide (Byetta®), sitagliptin and esomeprazole (Nexium®) expanded; medically necessary indications for 5HT3 antagonists, Actiq® and Fentora™ added to policy statement. Policy Guidelines updated and Rationale updated; references added</td>
</tr>
<tr>
<td>12/11/07</td>
<td>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.</td>
</tr>
<tr>
<td>04/08/08</td>
<td>Replace Policy - Policy updated with literature search by Pharmacy. Policy statement updated to include fibromyalgia as a medically necessary indication under Pregabalin. References added.</td>
</tr>
<tr>
<td>12/16/08</td>
<td>Replace Policy - Policy updated with literature search by Pharmacy. Policy statement updated to include the use of leukotrience modifiers for the treatment of allergic rhinitis refractory to nasal corticosteroids under the medically necessary indication. References added.</td>
</tr>
<tr>
<td>02/10/09</td>
<td>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</td>
</tr>
<tr>
<td>07/14/09</td>
<td>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.</td>
</tr>
<tr>
<td>08/11/09</td>
<td>Minor update to Policy Guidelines section - Added “agents” after pharmacologic for all 3 drugs in the policy guidelines section.</td>
</tr>
<tr>
<td>09/15/09</td>
<td>Minor updates - Corrected spelling errors, no other changes.</td>
</tr>
<tr>
<td>06/08/10</td>
<td>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.</td>
</tr>
<tr>
<td>05/10/11</td>
<td>Replace Policy - Policy updated with literature review; newly FDA-approved indication for Cymbalta in chronic musculoskeletal pain added to policy statements. No other changes.</td>
</tr>
<tr>
<td>06/26/12</td>
<td>Replace policy. Policy updated with literature review; no change in policy statements.</td>
</tr>
<tr>
<td>11/13/12</td>
<td>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.</td>
</tr>
<tr>
<td>11/26/12</td>
<td>Update Related Policies. Add 5.01.529.</td>
</tr>
<tr>
<td>02/11/13</td>
<td>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.</td>
</tr>
<tr>
<td>07/08/13</td>
<td>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.</td>
</tr>
<tr>
<td>12/06/13</td>
<td>Update Related Policies. Change title for 5.01.520.</td>
</tr>
<tr>
<td>03/17/14</td>
<td>Replace policy. Policy updated to include generic SNRI trial as a qualifier for coverage.</td>
</tr>
</tbody>
</table>
| 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.

12/13/16 Annual Review. No new information was found that would prompt a change to the existing policy criteria. Minor grammatical corrections were made to the reference section.

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037338 (07-2016)
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