Fibromyalgia Agents – Lyrica® (pregabalin) Savella® (milnacipran) Step Therapy and Quantity Limit Program Summary

This program applies to FlexRx Open, FlexRx Closed, GenRx Open, and Health Insurance Marketplace formularies.

This is a GenRx standard step therapy program.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business.

FDA APPROVED INDICATIONS AND DOSAGE[1,2]

<table>
<tr><th>Agents</th><th>Indications</th><th>Dosing and Administration</th></tr>
<tr><td>Lyrica
(pregabalin)

capsules,
oral solution</td><td>Neuropathic pain associated with diabetic peripheral neuropathy (DPN)

Postherpetic neuralgia (PHN)

Adjunctive therapy for adult patients with partial onset seizures

Fibromyalgia (FM)

Neuropathic pain associated with spinal cord injury (SCI)</td><td>For all indications, start dosing at 150 mg per day.
Dosing recommendations are:

<table>
<tr><th>Indication</th><th>Dosing Regimen (Doses/Day)</th><th>Maximum Daily Dose</th></tr>
<tr><td>Seizures</td><td>3 divided doses</td><td>Maximum dose of 600 mg/day</td></tr>
<tr><td>FM</td><td>2-3 divided doses</td><td>300 mg/day within 1 week;
Maximum 450 mg</td></tr>
<tr><td>PHN</td><td>2-3 divided doses</td><td>300 mg/day within 1 week;
Maximum 600 mg</td></tr>
<tr><td>DPN pain</td><td>2 divided doses</td><td>300 mg/day within 1 week</td></tr>
<tr><td>SCI pain</td><td>2 divided doses</td><td>300 mg/day within 1 week;
Maximum 600 mg</td></tr>
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</td></tr>
<tr><td>Savella
(milnacipran)

tablets,
titration pack</td><td>Management of fibromyalgia</td><td>Recommended dose is 100 mg/day (50 mg twice daily).
Dosing should be titrated according to the following schedule:
Day 1: 12.5 mg once
Days 2-3: 25 mg/day (12.5 mg twice daily)
Days 4-7: 50 mg/day (25 mg twice daily)
After Day 7: 100 mg/day (50 mg twice daily)

Based on individual patient response, the dose may be increased to 200 mg/day (100 mg twice daily). Doses above 200 mg/day have not been studied</td></tr>
</table>

CLINICAL RATIONALE

Fibromyalgia (FM)

Nonpharmacological therapy should be first-line therapy and then if there is a lack of effect, therapy should be individualized according to patient need, which may include pharmacological therapy. Pharmacologic therapies include: duloxetine, milnacipran, tramadol, pregabalin, and, cyclobenzaprine. Strength of recommendation for all these options is weak.[27,30] A review (2015) suggests pharmaceuticals (e.g., pregabalin, duloxetine, milnacipran) will provide clinically meaningful improvement without any major adverse events for a relatively small subset of patients only. In many other patients, the benefits do not outweigh the adverse effects, while the remainder do not experience any symptom improvement or even get worse.[27,31]

Pharmacological therapy should be guided by predominant symptoms that accompany pain. All patients should have a good therapeutic trial of a low-dose tricyclic compound (e.g., cyclobenzaprine, amitriptyline, or nortriptyline). Patients with comorbid depression or fatigue should next try a serotonin norepinephrine reuptake inhibitor (SNRI). Patients with comorbid anxiety or sleep issues should next try a gabapentinoid. It is often necessary to use several classes of drugs together. Use of opioids is discouraged. Nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen can be used to treat comorbid peripheral pain generators. [26]

Tramadol may be used in patients who require additional pain relief on a temporary basis for exacerbations or for patients who have inadequate pain control with other therapies.[32]

Neuropathic Pain

For patients with diabetic neuropathy, an antidepressant (e.g., amitriptyline, duloxetine, venlafaxine) or anticonvulsant (e.g., pregabalin) is recommend as initial therapy. Available evidence suggests these agents have similar modest benefit, though few high-quality comparative trials have been done. Among these options, the preference is to start with amitriptyline, particularly in younger healthier patients. Patients who fail to improve with a reasonable trial of one of these agents can be switched to monotherapy with another agent. For patients who do not improve on one drug, suggest combination therapy employing two drugs from different medication classes as the next step in the treatment paradigm. For patients who are unable to tolerate any of these drugs, alternative treatments include capsaicin cream, lidocaine patch, alpha-lipoic acid, isosorbide dinitrate topical spray, and transcutaneous electrical nerve stimulation.[33]

A meta-analysis (2015; 225 RCTs) evaluated pharmacotherapy for treatment of neuropathic pain (including peripheral diabetic neuropathy). Studies published in peer-reviewed journals reported greater effects than did unpublished studies. Trial outcomes were generally modest: combined NNTs (50% pain relief) were 6.4 for SNRIs, mainly including duloxetine (9 of 14 studies); 7.7 for pregabalin; 7.2 for gabapentin, and 10.6 for capsaicin high-concentration patches. NNTs were lower for tricyclic antidepressants (TCA), strong opioids, tramadol, and botulinum toxin A, and undetermined for lidocaine patches. Based on grade, final quality of evidence was moderate or high for all treatments apart from lidocaine patches; tolerability and safety, and values and preferences were higher for topical drugs; and cost was lower for TCAs and tramadol. These findings permitted a strong recommendation for use and proposal as first-line treatment in neuropathic pain for TCAs, SNRIs, pregabalin, and gabapentin; a weak recommendation for use and proposal as second line for lidocaine patches, capsaicin high-concentration patches, and tramadol; and a weak recommendation for use and proposal as third line for strong opioids and botulinum toxin A. Topical agents and botulinum toxin A are recommended for peripheral neuropathic pain only.[29]

Several societies and associations have strong recommendations for TCAs, gabapentin, pregabalin, and SNRI antidepressants (duloxetine [most studied], venlafaxine) as first-line therapies.[28]

Dworkin et al.[18] states that most randomized controlled trials of chronic neuropathic pain have examined only two pain syndromes, diabetic peripheral neuropathy and postherpetic neuralgia. These authors suggest that while the applicability of the results of clinical trials for one chronic neuropathic pain syndrome to others cannot be determined, most of the first-line therapies have been tested with multiple types of neuropathic pain and have shown similar results[18]

Generally, guidelines and reviews on treatment of neuropathic pain have not been consistent regarding their placement of anticonvulsants as first-, second-, or third-line treatment. Some guidelines and reviews recommend pregabalin and gabapentin [off-label] as first- or second-line treatment. Carbamazepine and lamotrigine [both off-label] have been considered second- or third-line treatments for neuropathic pain. TCAs (e.g. amitriptyline) are often recommended as a first-line treatment for neuropathic pain.[9-23]

American Academy of Neurology (AAN) recommendations for treatment of painful diabetic neuropathy include pregabalin (level A evidence, established as effective); and gabapentin, sodium valproate, venlafaxine, duloxetine, amitriptyline, dextromethorphan, maprotiline, tramadol, oxycodone, capsaicin, isosorbide dinitrate, electrical stimulation, percutaneous nerve stimulation (level B evidence, considered probably effective).[7]

A review (2010) suggests primary agents for treatment of painful diabetic neuropathy include TCAs, anticonvulsants, SNRIs, opiates, and topical medications. Although complete relief is ideal, pain reduction of only 30 to 50 percent can be expected in most patients taking maximal doses of medication. TCAs (amitriptyline, nortriptyline) are recommended as first-line therapy for painful diabetic neuropathy in appropriate patients. If TCAs are contraindicated, newer anticonvulsants (gabapentin, pregabalin) are considered. SNRIs may be used if first line agents are unsuccessful.[8]

Guidelines[18,22] consider TCAs, gabapentin, pregabalin, or tramadol, as effective first-line medications for treatment of neuropathic pain associated with spinal cord injury; lamotrigine and opioids may be effective in some patients.[18,22] Guidelines from the European Federation of Neurological Societies (EFNS), American Association of Clinical Endocrinologists (AACE), and the AAN/Neuromuscular and Electrodiagnostic Medicine/Physical Medicine and Rehabilitation recommend both pregabalin and gabapentin as first line treatment for peripheral neuropathy (included diabetic peripheral neuropathy, and post herpetic neuralgia.[22,24,25] The guidelines consider both gabapentin and pregabalin to be equal in efficacy and one is not preferred over the other.[22,25]

Seizure Disorders
According to guidelines from the American Academy of Neurology (AAN)/American Epilepsy Society (EPS), the National Institute for Clinical Excellence (NICE), and the International League Against Epilepsy (ILAE) the initial choice of an antiepileptic drug (AED) is dependent on the seizure type and the individual patient characteristics.[3-6]

Safety
Pregabalin has the following contraindication:[1]

- Known hypersensitivity to pregabalin or any of its components

Milnacipran has the following contraindication:[2]

- Do not use MAOIs intended to treat psychiatric disorders with milnacipran or within 5 days of stopping treatment with milnacipran. Do not use milnacipran within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start milnacipran in a patient who is being treated with linezolid or intravenous methylene blue.

Milnacipran has the following black box warning:[2]

- Increased risk of suicidal ideation, thinking, and behavior in children, adolescents, and young adults taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders
- Milnacipran is not approved for use in pediatric patients

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Fibromyalgia Agents (Lyrica®/Savella®) Step Therapy and Quantity Limit

OBJECTIVE
The intent of the Fibromyalgia Agents (Lyrica/Savella) Step Therapy (ST) program is to encourage the use of cost-effective generic medications for treatment of fibromyalgia before use of Lyrica or Savella. The program allows use of Lyrica or Savella when the patient has had prior use of generic duloxetine, amitriptyline, nortriptyline, desipramine, imipramine, gabapentin, cyclobenzaprine, venlafaxine, or tramadol. In addition, the program accommodates use of Lyrica for the treatment of seizure disorders. Requests for Lyrica or Savella will be reviewed when patient-specific documentation has been provided.

TARGET AGENTS
Lyrica® (pregabalin)
Savella® (milnacipran)

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Lyrica will be approved when ANY ONE of the following is met:
1. The patient has a diagnosis of a seizure disorder
   OR
2. The patient's medication history includes use of another anticonvulsant medication
   OR
3. The patient's medication history includes use of generic duloxetine, amitriptyline, nortriptyline, imipramine, desipramine, cyclobenzaprine, venlafaxine, gabapentin, or tramadol in the past 90 days
   OR
4. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to one of the prerequisite agents listed above

Savella will be approved when the following are met:
1. The patient's medication history includes use of generic duloxetine, amitriptyline, nortriptyline, imipramine, desipramine, cyclobenzaprine, venlafaxine, gabapentin, or tramadol in the past 90 days
   OR
2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to one of the prerequisite agents listed above

Length of Approval: 12 months

NOTE: If Quantity Limit program also applies, please refer to Quantity Limit documents.

Step Therapy Supplement

This program applies to FlexRx Closed, FlexRx Open, GenRx Closed, GenRx Open, Health Insurance Marketplace, FocusRx and KeyRx formularies.

Please note, this does not include or apply to quantity limit questions.

STEP THERAPY SUPPLEMENT
OBJECTIVE
The intent of the Step Therapy Supplement is to provide additional questions, to ensure compliance to MN Statute 62Q.184. These questions will apply if the step therapy component within a Prior Authorization or Step Therapy program is not able to be approved.

CONDITIONS FOR APPROVAL
The requested agent will be approved when ONE of the following are met:

1. The patient is currently being treated with the requested agent as indicated by ALL of the following:
    a. A statement by the prescriber that the patient is currently taking the requested agent
    AND
    b. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
    AND
    c. The prescriber states that a change in therapy is expected to be ineffective or cause harm

    OR
2. The patient's medication history include the required prerequisite/preferred agent(s) as indicated by:
    a. Evidence of a paid claim(s) within the past 999 days
    OR
    b. The prescriber has stated that the patient has tried the required prerequisite/preferred agent(s) in the past 999 days AND the required prerequisite/preferred agent(s) was discontinued due to lack of effectiveness or an adverse event

    OR
3. The prescriber has provided documentation that the required prerequisite/preferred agent(s) cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

Length of Approval: As per program specific criteria