



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 program is not implemented with auto-grandfathering.

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.

Program specific denial language for prerequisite step therapy component does not apply. Instead, supplemental program denial language will apply.

FDA APPROVED INDICATIONS AND DOSAGE^{1,2}

Agent	Indication	Dosage																		
Lyrica® (pregabalin) capsules, oral solution	Neuropathic pain associated with diabetic peripheral neuropathy (DPN)	For all indications, start dosing at 150 mg per day. Dosing recommendations are: <table border="1" style="margin-top: 10px;"> <thead> <tr> <th>Indication</th> <th>Dosing Regimen (Doses/Day)</th> <th>Maximum Daily Dose</th> </tr> </thead> <tbody> <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> </tbody> </table>	Indication	Dosing Regimen (Doses/Day)	Maximum Daily Dose	Seizures	3 divided doses	Maximum dose of 600 mg/day	FM	2-3 divided doses	300 mg/day within 1 week; Maximum 450 mg	PHN	2-3 divided doses	300 mg/day within 1 week; Maximum 600 mg	DPN pain	2 divided doses	300 mg/day within 1 week	SCI pain	2 divided doses	300 mg/day within 1 week; Maximum 600 mg
	Indication		Dosing Regimen (Doses/Day)	Maximum Daily Dose																
	Seizures		3 divided doses	Maximum dose of 600 mg/day																
	FM		2-3 divided doses	300 mg/day within 1 week; Maximum 450 mg																
	PHN		2-3 divided doses	300 mg/day within 1 week; Maximum 600 mg																
	DPN pain		2 divided doses	300 mg/day within 1 week																
	SCI pain		2 divided doses	300 mg/day within 1 week; Maximum 600 mg																
Postherpetic neuralgia (PHN)																				
Adjunctive therapy for adult patients with partial onset seizures																				
Fibromyalgia (FM)																				
Neuropathic pain associated with spinal cord injury (SCI)																				
Savella® (milnacipran) tablets, titration pack	Management of fibromyalgia	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																		

CLINICAL RATIONALE

Fibromyalgia

Fibromyalgia is a chronic pain disorder that is challenging to treat. Effective interventions include nonpharmacologic and pharmacologic therapies with a multidisciplinary, individualized approach. Treatment of fibromyalgia is directed at reducing the major symptoms, which includes chronic widespread pain, fatigue, insomnia, and cognitive dysfunction. Initial approach should be for patient education regarding fibromyalgia, good sleep hygiene, treatment approaches, and the effects of poor sleep on pain and treating comorbidities that may contribute to symptoms, including mood and sleep disorders. Exercise is also recommended, including aerobic conditioning, stretching, and strengthening.²⁻⁵

Pharmacological treatments that are the best studied and have been used most consistently in the treatment of fibromyalgia are certain antidepressants and selected anticonvulsants. Antidepressants include widely available tricyclic antidepressants (TCAs), including amitriptyline, desipramine, and serotonin and norepinephrine reuptake inhibitors (SNRI), including duloxetine and milnacipran. Cyclobenzaprine, gabapentin, and pregabalin are also used to treat fibromyalgia.²⁻⁵ A large study using insurance claims data from the United States found that only 31 percent of fibromyalgia patients initiated treatment with one of the medications listed in the American College of Rheumatology (ACR) guidelines. These medications included pregabalin, gabapentin, duloxetine, milnacipran, cyclobenzaprine, tramadol, amitriptyline, and venlafaxine. Many of these subjects did not receive the recommended dose, and adherence was suboptimal for each of the ACR recommended medications. Approximately 50 percent of patients received a second analgesic within one year.^{6,7} Analgesics, such as acetaminophen or tramadol, alone or in combination in patients who require additional pain relief on a temporary basis for a disease exacerbation or in whom other therapies have been inadequate for controlling pain.⁶

Neuropathic Pain

Diabetic peripheral neuropathy (DPN) develops as a late manifestation of uncontrolled or long-standing diabetes and is the most prevalent chronic complication of diabetes. Distal symmetric polyneuropathy (DSPN) is characterized by burning pain, paresthesias, and numbness that follows a stocking-glove pattern and progresses proximally. Poorly controlled blood glucose levels, especially greater variation in glucose levels, contribute to the occurrence and severity of painful DPN.⁸ DSPN is the most important cause of foot ulceration and a prerequisite to the development of Charcot neuroarthropathy (CN), which are both recognized as late complications of DSPN. The late complications also drive amputation risk and economic costs of diabetic neuropathy and are also predictors of mortality. DSPN is also a major contributor to falls and fractures.⁹

Due to lack of treatments that target the underlying nerve damage, prevention is the key component of diabetes care. Prevention of diabetic neuropathies focuses on glucose control and lifestyle modifications, which includes dietary modifications and exercise.⁸ Optimal glucose control is considered the cornerstone for the treatment of diabetes and its complications. Intensive glucose control has been shown to prevent the development of peripheral neuropathy. For patients with diabetic neuropathy, foot care is important to prevent ulceration, infection, and amputation.^{9,10}

There are several pharmacological options for DPN. The American Diabetes Association (ADA), American Academy of Neurology (AAN), and American Academy of Family Physicians (AAFP) recommend use of pregabalin and duloxetine as first line therapy for painful diabetic neuropathy.⁸⁻¹⁰ AAFP recommends gabapentin as the first-line alternative.⁹ Other treatment options include antidepressants (e.g., amitriptyline, nortriptyline, desipramine, imipramine, venlafaxine), anticonvulsants (e.g. gabapentin, sodium valproate), and capsaicin cream.⁸⁻¹⁰ Tramadol has been shown to be effective in the treatment of DPN. Although tramadol has a

lower potential for abuse compared with other opioids, given the safety concern, it is not recommended as first or second line treatment.⁹

Seizure Disorders

Management of patients with epilepsy is focused on three main goals: controlling seizures, avoiding treatment side effects, and maintaining or restoring quality of life. An optimal treatment plan is derived following an accurate diagnosis of the patient's seizure type(s), objective measurement of the intensity and frequency of the seizures, awareness of the medication side effects, and an evaluation of disease-related psychosocial problems.

Antiseizure drug treatment is generally started after two or more unprovoked seizures, because the recurrence proves that the patient has a substantially increased risk for repeated seizures, well above the 50 percent. Approximately half of patients with a new diagnosis of epilepsy will become seizure free with the first antiseizure drug prescribed. Tolerability of side effects is important as efficacy in determining the overall effectiveness of treatment. No single antiseizure drug is optimal for every patient or even most patients. The selection of therapy for treating seizures must be individualized for the patient based on drug effectiveness for the seizure type or types, potential adverse effects, interactions with other medications, comorbid medical conditions, especially but not limited to hepatic and renal disease, age, gender, childbearing plans, lifestyle and patient preferences, and cost.¹¹

REFERENCES

1. Lyrica prescribing information. Pfizer/Parke-Davis. December 2016.
2. Savella prescribing information. Forest Pharmaceuticals, Inc. December 2017.
3. Goldenberg, Don L., MD, et al. Initial Treatment of Fibromyalgia in Adults. UpToDate. Last Updated November 2018.
4. Bhana, Suleman, MD. Fibromyalgia. American College of Rheumatology. Available at: <https://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Fibromyalgia>. Accessed January 2019.
5. Dymon, Tara E., PharmD, BCACP, et al. Fibromyalgia. *Neurologic and Psychiatric Care I*. ACSP 2015. Available at: https://www.accp.com/docs/bookstore/acsap/a15b1_m1sample.pdf. Accessed January 2019.
6. Liu, Y, et al. Treatment Patterns Associated with ACR- Recommended Medications in the Management of Fibromyalgia in the United States. *J Managed Care Spec Pharm*. 2016 Mar;22(3):263-271.
7. Goldenberg, Don L., et al. Treatment of Fibromyalgia in Adults Not Responsive to Initial Therapies. UpToDate. Last updated June 2018. Literature review through December 2018.
8. Snyder, Matthew J, DO, et al. Treating Painful Diabetic Peripheral Neuropathy: An Update. *American Family Physicians*. 2016; 94 (3):227-234.
9. Pop-Busui, Rodica, et al. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. *Diabetes Care*. 2017; 40: 136-154.
10. Feldman, Eva L., MD, PhD, et al. Treatment of diabetic neuropathy. UpToDate. Last Updated November 2018.
11. Schachter, Steven C, MD, et al. Overview of the Management of Epilepsy in Adults. UpToDate. Last updated September 2018. Literature review current through December 2018.

Fibromyalgia Agents -Lyrica, Savella Step Therapy and Quantity Limit

TARGET AGENTS

Lyrica® (pregabalin)

Savella® (milnacipran)

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Lyrica will be approved when 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
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 ALL of the prerequisite agents listed above

Length of Approval: 12 months

Savella will be approved when ONE of the following is 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 ALL 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