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

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

This is a GenRx Standard 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]

Agent(s)	Indication(s)	Dosage
Lyrica® (pregabalin) Capsule[a] Oral solution[a]	Neuropathic pain associated with diabetic peripheral neuropathy (DPN) Postherpetic neuralgia (PHN) Adjunctive therapy for the treatment of partial-onset seizures in patients 1 month of age and older Fibromyalgia (FM) Neuropathic pain associated with spinal cord injury (SCI)	For adult indications, start dosing at 150 mg per day. Dosing recommendations: • DPN Pain: 3 divided doses up to a maximum of 300 mg/day • PHN: 2-3 divided doses up to a maximum of 600 mg/day • Seizures, adult: 2-3 divided doses up to a maximum of 600 mg/day • Seizures, pediatric, 30 kg and over: 2-3 divided doses up to a maximum of 10 mg/kg/day • Seizures, pediatric, less than 30 kg: 2-3 divided doses, up to 14 mg/kg/day • FM: 2 divided doses up to a maximum of 450 mg/day • SCI pain: 2 divided doses, up to a maximum of 600 mg/day
Savella® (milnacipran) Tablet Titration pack	Management of fibromyalgia Limitation of use: Savella is not approved for use in pediatric patients	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.

a – generic equivalent available

CLINICAL RATIONALE

Fibromyalgia

Fibromyalgia is a chronic condition with unknown etiology. It is characterized by generalized body pain, fatigue, sleep disturbance, impaired cognition, and anxiety. Diagnosis is often made by exclusion of other conditions such as neurological syndromes and depression. There is no clear specific pathophysiological therapeutic target. Various guidelines for treatment exist and they are not in agreement. There has been an increase in non-pharmacologic therapies discussed in the guidelines. Pharmacologic therapy varies, including classical analgesics, antidepressants, and anticonvulsants. Commonly used agents include tricyclic antidepressants (TCAs), pregabalin, gabapentin, serotonin and norepinephrine reuptake inhibitors (SNRI), selective serotonin reuptake inhibitors (SSRI), tramadol, and cyclobenzaprine.[3]

Neuropathic Pain

Diabetic Peripheral Neuropathy

Diabetic peripheral neuropathy (DPN) develops as a late manifestation of uncontrolled or long-standing diabetes. DPN patients may develop distal symmetric polyneuropathy (DSPN), which 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.[4]

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. For patients with diabetic neuropathy, foot care is important to prevent ulceration, infection, and amputation.[4]

There are several pharmacological options for DPN. The American Diabetes Association (ADA) and American Academy of Family Physicians (AAFP) recommend use of pregabalin and duloxetine as first line therapy for painful diabetic neuropathy. The ADA recommends gabapentin as the first-line alternative, though AAFP considers it a first-line therapy.[4,5] Other treatment options include antidepressants (e.g., amitriptyline, nortriptyline, desipramine, imipramine, venlafaxine), anticonvulsants (e.g. lamotrigine, topiramate, valproate), and topical agents (e.g., capsaicin cream, lidocaine 5% patch).[4,5] 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.[4]

Postherpetic Neuralgia

Postherpetic neuralgia (PHN), the most common complication of herpes zoster, is defined as pain in a dermatomal distribution that is sustained for at least 90 days after the rash. It occurs in approximately 10-20% of patients with herpes zoster, and 80% of cases occur in patients 50 years or older. PHN is caused by nerve damage secondary to an inflammatory response induced by viral replication within a nerve.[6] Gabapentin, pregabalin, and the TCAs are considered first-line therapies, along with the topical therapies of lidocaine patch and capsaicin cream. Tramadol is considered a third-line option.[6]

Neuropathic Pain due to Spinal Cord Injury

Spinal cord injury (SCI) is an injury to the spinal cord that leads to varying degrees of motor and/or sensory deficits and paralysis. Chronic neuropathic pain is common and contributes to reduced quality of life. First-line drugs commonly used are amitriptyline, gabapentin, and pregabalin. Alternative agents are tramadol and duloxetine.[7]

Seizure Disorders

The occurrence of a single seizure does not always require initiation of antiepileptic drugs (AEDs). In the absence of risk factors, physicians should consider delaying used of AEDs until a second seizure occurs. Treatment should begin with monotherapy.[8] Pregabalin has FDA approval for adjunctive therapy for the treatment of partial-onset seizures in patients 1 month of age and older.[1]

Safety

Savella carries a black box warning for suicidality and antidepressant drugs.

- 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.
- Savella is not approved for use in pediatric patients.[2]

References

1. Lyrica prescribing information. Pfizer/Parke-Davis. June 2020.
2. Savella prescribing information. Forest Pharmaceuticals, Inc. June 2019.
3. Kia S, Choy E. Update on Treatment Guideline in Fibromyalgia Syndrome with Focus on Pharmacology. *Biomedicines* 2017;5(2):1-24. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5489806/ Accessed 11/4/2021.
4. Pop-Busui, Rodica, et al. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. *Diabetes Care.* 2017; 40: 136-154. Available at: https://care.diabetesjournals.org/content/40/1/136. Accessed November 4,2021.
5. Snyder, Matthew J, DO, et al. Treating Painful Diabetic Peripheral Neuropathy: An Update. *American Family Physicians*. 2016; 94 (3):227-234. Available at: https://www.aafp.org/afp/2016/0801/p227.html Accessed November,4, 2021.
6. Saguil A, Kane S, Mercado M, Lauters R. Herpes Zoster and Postherpetic Neuralgia: Prevention and Management. *Am Fam Physician* 2017;96(10):656-663. Available at: https://www.aafp.org/afp/2017/1115/p656.html. Accessed November 4, 2021.
7. Hagen EM, Rekand T. Management of Neuropathic Pain Associated with Spinal Cord Injury. *Pain Ther* 2015;4(1):51-65. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4470971/#__ffn_sectitle. Accessed November 4, 2021.
8. Liu G, Slater N, Perkins A. Epilepsy: Treatment Options. *American Family Physician* 2017; 95(2):87-96. Available at: https://www.aafp.org/afp/2017/0715/p87.html Accessed November 4, 2021.

Fibromyalgia Agents -Lyrica, Savella Step Therapy

TARGET AGENT(S)

Lyrica® (pregabalin)[a]
Savella® (milnacipran)
a – available as a generic; included as a prerequisite in the step therapy program

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Lyrica will be approved when ONE of the following is 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 has a diagnosis of a seizure disorder

    OR
3. The patient's medication history includes use of another anticonvulsant within the past 90 days

    OR
4. The patient's medication history includes use of generic duloxetine, amitriptyline, nortriptyline, imipramine, desipramine, cyclobenzaprine, venlafaxine, gabapentin, pregabalin or tramadol within the past 999 days

    OR
5. BOTH of the following:
    A. The prescriber has stated that the patient has tried generic duloxetine, amitriptyline, nortriptyline, imipramine, desipramine, cyclobenzaprine, venlafaxine, gabapentin, pregabalin, or tramadol
    AND
    B. Generic duloxetine, amitriptyline, nortriptyline, imipramine, desipramine, cyclobenzaprine, venlafaxine, gabapentin, pregabalin, or tramadol was discontinued due to lack of effectiveness or an adverse event

    OR
6. The patient has an intolerance or hypersensitivity to generic duloxetine, amitriptyline, nortriptyline, imipramine, desipramine, cyclobenzaprine, venlafaxine, gabapentin, pregabalin, or tramadol

    OR
7. The patient has an FDA labeled contraindication to generic duloxetine, amitriptyline, nortriptyline, imipramine, desipramine, cyclobenzaprine, venlafaxine, gabapentin, pregabalin, AND tramadol

    OR
8. The prescriber has provided documentation that generic duloxetine, amitriptyline, nortriptyline, imipramine, desipramine, cyclobenzaprine, venlafaxine, gabapentin, AND tramadol 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: 12 months

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

Savella will be approved when ONE of the following is 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 includes use of generic duloxetine, amitriptyline, nortriptyline, imipramine, desipramine, cyclobenzaprine, venlafaxine, gabapentin, pregabalin, or tramadol within the past 999 days

    OR
3. BOTH of the following:
    A. The prescriber has stated that the patient has tried generic duloxetine, amitriptyline, nortriptyline, imipramine, desipramine, cyclobenzaprine, venlafaxine, gabapentin, pregabalin, or tramadol
    AND
    B. Generic duloxetine, amitriptyline, nortriptyline, imipramine, desipramine, cyclobenzaprine, venlafaxine, gabapentin, pregabalin, or tramadol was discontinued due to lack of effectiveness or an adverse event

    OR
4. The patient has an intolerance or hypersensitivity to generic duloxetine, amitriptyline, nortriptyline, imipramine, desipramine, cyclobenzaprine, venlafaxine, gabapentin, pregabalin, or tramadol

    OR
5. The patient has an FDA labeled contraindication to generic duloxetine, amitriptyline, nortriptyline, imipramine, desipramine, cyclobenzaprine, venlafaxine, gabapentin, pregabalin, AND tramadol

    OR
6. The prescriber has provided documentation that generic duloxetine, amitriptyline, nortriptyline, imipramine, desipramine, cyclobenzaprine, venlafaxine, gabapentin, pregabalin, AND tramadol 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: 12 months

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