Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCCNS018.0824	**CENTRAL NERVOUS SYSTEM DRUGS** **SAVELLA®** (milnacipran tablets)
Effective Date: 10/1/2024	**Review/Revised Date**: 04/10, 04/11, 10/11, 08/12, 08/13, 08/14, 08/15, 07/16, 07/17, 06/18, 07/19, 06/20, 07/21, 07/22, 07/23, 07/24 (JLS)
Original Effective Date: 10/09	**P&T Committee Meeting Date**: Date: 10/09, 04/10, 04/11, 10/11, 08/12, 08/13, 08/14, 10/14, 08/15, 08/16, 08/17, 08/18, 08/19, 02/20, 08/21, 08/22, 08/23, 08/24
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

Coverage for Medicaid is limited to a condition that has been designated a covered line-item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services when all applicable indication-specific criteria below are met. The Early and Periodic Screening, Diagnostic and Treatment (EPSDT) benefit provides comprehensive and preventive health care services for children and adolescents up to their 21st birthday who are enrolled in Medicaid. Management of unfunded conditions falls under this benefit when they impact the ability to grow, develop or participate in school and the applicable indication-specific criteria below are met.

REQUIRED MEDICAL INFORMATION:
For initiation of therapy for fibromyalgia: Documentation of an adequate trial and failure (defined as adherence to at least six weeks of therapy without improvement in symptoms), intolerance, or contraindication to the following:
1. Gabapentin OR pregabalin (Lyrica®)

AND

2. One of the following:
    a. A Selective serotonin reuptake inhibitors/Serotonin-norepinephrine reuptake inhibitors (SSRI)/(SNRI) (such as, fluoxetine, duloxetine)
    b. A tricyclic antidepressant (TCA) medication (such as, amitriptyline)

For patients established on therapy, defined as consistent use for at least one year: documentation of improvement in symptoms.

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS: N/A

COVERAGE DURATION:
Authorization will be approved until no longer eligible with the plan, subject to formulary or benefit changes.

QUANTITY LIMITS:
One pack (55 tablets) per 365 days for the Titration Pack.
60 tablets per 30 days for the 12.5 mg, 25 mg, 50 mg and 100 mg tablet strengths.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Milnacipran is a selective serotonin and norepinephrine reuptake inhibitor (SNRI) approved by the FDA for the treatment of fibromyalgia (FM). The exact mechanism of action is unknown but is believed to be related to its potential to correct an imbalance in serotonergic and noradrenergic activity in the central nervous system. Peer reviewed randomized controlled trials have demonstrated that milnacipran is more effective than placebo in the treatment of fibromyalgia. There are no head-to-head trial data available to review the drug's effectiveness compared to other active agents.

FDA APPROVED INDICATIONS: Fibromyalgia

POSITION STATEMENT:

Savella® has been studied in two doses 100 and 200 mg/day. The recommended dose is 100 mg/day and Savella® will be approved for a maximum daily dose of 200 mg.

Because of the lack of evidence of long-term efficacy and tolerability information, and the availability of numerous other cost-efficient agents, milnacipran is not first line therapy for fibromyalgia.

Milnacipran is selective serotonin and norepinephrine reuptake inhibitor, similar to some drugs used for the treatment of depression and other psychiatric disorders. The prescribing information for milnacipran contains a safety warning regarding the risk of suicidality similar to other antidepressant drugs. Patients started on milnacipran should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior.

In clinical trials milnacipran improved pain and global wellbeing in fibromyalgia more than placebo. Two pivotal trials noted the safety and efficacy of Savella® for the treatment of fibromyalgia[1,2]. (Please see Appendix for summary of the studies). There are several limitations and threats to validity of these studies including:

- Composite primary outcomes that limit ability to establish the clinical significance of the results
- Short term studies with lack of benefit seen at later time points
- High dropout rate in both studies (33-42%)
- High placebo response rates
- Lack of diversity in the study populations

Amitriptyline[3-4], fluoxetine[5,6], cyclobenzaprine[7], gabapentin[8], pregabalin[9-10] and duloxetine[11-12] have all been studied and have shown similar efficacy in the treatment of fibromyalgia. This has been confirmed by reviews completed by the American Pain Society[13] and EULAR[14]. No head to head trials have been completed. There is no evidence to support the superiority of milnacipran over these agents. Duloxetine (Cymbalta®, pregabalin (Lyrica®) and milnacipran (Savella®) are FDA approved for treatment of fibromyalgia. The efficacy and safety of combining treatment medications is unknown. Savella® carries the same warning of other SNRI medications of increased risk of suicidal ideation, thinking and behavior. The safety and effectiveness of milnacipran for fibromyalgia has not been established in patients less than 17 years of age.

Fibromyalgia is considered a “below the line” diagnosis for Medicaid.

REFERENCES AND RESOURCES:

1. Clauw DJ, Mease P, Palmer RH, et al. Milnacipran for the Treatment of Fibromyalgia in Adults: A 15-week, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose Clinical Trial. *Clin Thera* 2008;30:1988-2004.
2. Mease PJ, Clauw DJ, Gendreau RM, 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.
3. Carette S, et al. Evaluation of amitriptyline in primary fibrositis. A double-blind placebo controlled trial. *Arthritis Rheum* 1986:29:655-9.
4. Scudds Ra, et al. Improvements in pain responsiveness in patients with fibrositis after successful treatment with amitriptyline. *Journal of Rheumatology* 1989: Suppl 19:98-103.
5. Wolf F, et al. A double-blind placebo-controlled trial of fluoxetine in fibromyalgia. *Scand J Rehumatol* 1994;23:255-9.
6. Arnold LM, et al. A randomized, placebo-controlled, double-blind, flexible dose study of fluoxetine in the treatment of women with fibromyalgia. *American J Med* 2002;112:191-7.
7. Carette, S, Bell,MJ, Reynolds WJ, et al. Comparison of amitriptyline, cyclobenzaprine and placebo in the treatment of fibromyalgia. A randomized, double-blind clinical trial. (abstract). *Arthritis Rheum*. 1994 Jan;37(1):32-40.
8. Arnold LM, Goldenberg DL. Gabapentin in the treatment of fibromyalgia: a randomized, double-double blind, placebo-controlled, multicenter trial. *Arthritis & Rheumatism*. 2007 Apri;56(4):1336-44.
9. Crofford LJ, Rowbotham MC, et al. Pregabalin for the treatment of fibromyalgia syndrome. *Arthritis and Rheumatism* 2005 Apr;(52):1264-1273.
10. Mease PJ, et al. A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. *J Rheumatol*. 2008 Mar;35(3):502-14.
11. Arnold LM, et al. A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. *Arthritis Rheum*. 2004 Sep;50(9):2974-84.
12. Russell IJ, et al. Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: Results from a 6-month, randomized, double-blind, placebo-controlled, fixed-dose trial. *Pain*. 2008 Jun;136(3):432-44.
13. Goldenberg DL, Burckhardt C, Crofford L et al. Management of Fibromyalgia Syndrome. *JAMA* 17 Nov 2004. 292(19):2388-2395.
14. Carville SF, Arendt-Nielsen S, Bliddal H, et al EULAR evidence based recommendations for the management of fibromyalgia syndrome. *Ann Rheum Dis Apr2008;67(4):536-41.*
15. Savella® [package insert]. St, Louis, MO: Forest Pharmaceuticals, Inc.; 2017 Dec.

16. Lyrica® [package insert]. New York, NY: Pfizer-Parke Davis; Oct. 2010.
17. Cymbalta® [package insert]. Eli Lilly and Company. Indianapolis, Indiana; Nov. 2010.
18. Milnacipran. In: Facts and Comparisons, Clin-eguide® [Internet database]. St. Louis, MO: Wolters Kluwer Health, Inc., Updated periodically.
19. Milnacipran. In: DRUGDEX® System [Internet database]. Greenwood Village, CO: Thompson Reuters (Healthcare) Inc., Updated periodically.

Appendix

Summary of two pivotal published studies for milnacipran use in fibromyalgia

1. Clauw DJ, Mease P, Palmer RH, et al. Milnacipran for the Treatment of Fibromyalgia in Adults: A 15-week, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose Clinical Trial. Clin Thera 2008;30:1988-2004.
   - 1196 patients were randomized to receive placebo (n=405) vs. milnacipran 100mg (n=401) vs. milnacipran 200mg (n=401) daily for 15 weeks.
   - *Inclusion Criteria*: Adult patients (18 -70 years old) who met the American College of Rheumatology criteria for fibromyalgia and who were willing to withdraw from CNS-active therapies commonly used to treat FM and who had a raw score of ≥4 on the physical function component of the FIQ and had a mean visual analog scale (VAS) pain score of ≥40 on a scale from 0 to 100 at the end of the baseline period.
   - *Exclusion Criteria*: severe psychiatric illness; a current major depressive episode; significant suicide risk; abuse of alcohol, benzodiazepines or other drugs; a history of behavior that would prohibit compliance for the duration of the study; active cardiovascular, pulmonary, hepatic, renal, gastro-intestinal or autoimmune disease; current systemic infection; active cancer (except basal cell carcinoma); unstable endocrine disease; severe sleep apnea; prostate enlargement or other genitourinary disorder (male patients); or pregnancy or breastfeeding (female patients).
   - *Primary Outcomes*: There were two primary efficacy endpoints. The first was a fibromyalgia composite responder rate at week 15, that consisted of 3 components: the mean of morning-recall VAS pain scores recorded on the PED during the 2-week interval before the clinic visit at week 15, the global status as indicated by the PGIC at week 15 and the change in physical function as indicated by the SF-36 PCS score. Patients were classified as FM composite responders if they had a ≥30% improvement from baseline in the PED morning-recall VAS pain score, a PGIC rating of much improved or

very much improved at week 15, and a ≥6-point improvement in the SF-36 PCS score from baseline to week 15.
The second primary outcome measure was the fibromyalgia pain composite responder rate based on the PED pain and PGIC assessments at week 15, with FM pain responders defined as those who met the response criteria for these 2 components.

- *Secondary Outcomes*: included the time-weighted averages of the individual components of the composite responder analyses (calculated for the weekly mean of PED morning-recall pain scores, from weeks 4 to 15, PGIC scores from weeks 3 to 15 and SF-36 PCS scores from week 3 to 15), weekly averages of the PED weekly-recall pain scores, and VAS paper assessments of pain recalled over 24 hours and 7 days.
- *Results*: At week 15, a statistically significant greater proportion of patients treated with either milnacipran 100mg/day (p=0.01) or 200mg/day (p=0.02) met all 3 criteria for an FM composite response compared to those who received placebo (BOCF).
  Also a statistically significant greater proportion of patients treated with either milnacipran 100mg/day (p=0.03) or 200mg/day (p=0.04) met all 3 criteria for an FM pain composite response compared to those who received placebo (BOCF).
- *Limitations*: 18% drop out rate, short time period (15 weeks) unable to verify long term drug efficacy in a chronic disease state, no other meds for pain, excluded patients with depression, primary endpoints were composites – individual items (e.g. pain, physical function, fatigue) were secondary endpoints. Strict criteria for selection of study population and lack of diversity may limit generalizability of results.

2. Mease PJ, Clauw DJ, Gendreau RM, 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.
   - 888 patients were randomized to receive placebo (n=223) vs. milnacipran 100mg (n=224) vs. milnacipran 200mg (n=441) daily for 27 weeks.
   - *Inclusion Criteria*: Adult patients (18 -70 years old) who met the American College of Rheumatology criteria for fibromyalgia and who were willing to withdraw from CNS-active therapies commonly used to treat FM (including antidepressants, sedative-hypnotic agents, muscle relaxants and centrally-acting analgesics), willing to use a contraceptive if female, and who had a raw score of ≥4 on the physical function component of the FIQ and had a mean visual analog scale (VAS) pain score of ≥40 on a scale from 0 to 100 at the end of the baseline period.

- *Exclusion Criteria*: severe psychiatric illness; a current major depressive episode; significant suicide risk; abuse of alcohol, benzodiazepines or other drugs; active cardiovascular, respiratory, liver, renal, active peptic ulcer or autoimmune disease; current systemic infection; active cancer or chemotherapy; endocrine disease; severe sleep apnea; inflammatory bowel disease; or genitourinary disorders.
- *Primary Outcomes*: There were two primary efficacy endpoints. The first was a fibromyalgia composite responder rate assessed at weeks 15 and 27, defined as the percentage of patients who currently met all of the following 3 criteria: (1) a ≥30% improvement from baseline in the mean of morning-recall VAS pain scores recorded on the PED during the 14 days before and including study visit days, (2) a Patient Global Impression of Change rating of much improved or very much improved at week 27, and (3) a ≥6-point improvement in the SF-36 Physical Component Summary score from baseline to the end of the study.
- The second primary outcome measure was a fibromyalgia pain composite responder rate assessed at weeks 15 and 27 based on the pain improvement and PGIC thresholds listed above.
- *Secondary Outcomes*: The secondary measures examined the influence of milnacipran on the following domains: pain severity, patient global impression of change, physical and mental function, impact of disease, fatigue, severity of depressive symptoms, sleep quality, general health-related quality of life, self-reported cognitive impairment and quality of sexual experiences.
- *Results*: At week 15, a statistically significant greater proportion of patients treated with either milnacipran 100mg/day (p=0.028) or 200mg/day (p=0.017) met all 3 criteria for an FM composite response compared to those who received placebo (BOCF).
  Also a statistically significant greater proportion of patients treated with milnacipran 200mg/day (26.8% / p=0.032) met all 3 criteria for an FM pain composite response compared to those who received placebo (BOCF). In the patients treated with 100mg/day (27.2% / p=0.056) there was no statistical significance to the difference from placebo (19.3%) (BOCF).
  At 27 weeks a modified BOCF/LOCF method was used to determine the results. BOCF values were used for patients prematurely discontinuing the study before week 15 and LOCF for those completing the study through week 15 but prematurely discontinuing before week 27.
  Using this method, only the patients treated with milnacipran 200mg/day (25.6% / p=0.034) met all three criteria for a significant difference in the FM pain composite responder rate from placebo (18.4).

An observed case (OC) analysis was also determined at the 15 week and 27 week visits for those who completed the study through to week 27. In these patients, the percentage who met criteria as FM composite responders at the end of the study was significantly higher only for those taking milnacipran 200mg/day (31.9% / p=0.017) vs. placebo (19.4%).
A significant difference was seen in the FM pain composite responder rate for both milnacipran treatment groups: milnacipran 100mg/day (43.8% / p=0.021), milnacipran 200mg/day (43.8% / p=0.021) vs. placebo (27.9%).

- *Limitations*: 42% drop out rate, short time periods (15 weeks and 27 weeks) unable to verify long term drug efficacy in a chronic disease state, no other meds for pain, excluded patients with depression, primary endpoints were composites – individual items (e.g. pain, physical function, fatigue) were secondary endpoints. Strict criteria for selection of study population and lack of diversity may limit generalizability of results.