Clinical Policy: Milnacipran (Savella)

Reference Number: CP.PMN.125
Effective Date: 08.01.12
Last Review Date: 05.23
Line of Business: Commercial, HIM, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Milnacipran (Savella®) is a selective serotonin and norepinephrine reuptake inhibitor (SNRI).

FDA Approved Indication(s)

Savella is indicated for the management of fibromyalgia. Savella is not approved for use in pediatric patients.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Savella is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Fibromyalgia (must meet all)**:**

1. Diagnosis of fibromyalgia;
2. Age ≥ 18 years;
3. Member meets one of the following (a or b):
   a. Failure of a 30-day trial of duloxetine at up to maximally indicated doses in the last 180 days;
   b. Member has contraindication or intolerance to duloxetine, and failure of a 30-day trial of any tricyclic antidepressant (TCA) or cyclobenzaprine at up to maximally indicated doses in the last 180 days, unless clinically significant adverse effects are experienced, member's age is ≥ 65 years, or all agents are contraindicated;
4. Dose does not exceed both (a and b):
   a. 200 mg per day;
   b. 2 tablets per day.

Approval duration:
Medicaid/HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

B. Depression (off-label) (must meet all)**:**

1. Diagnosis of depression;
2. Age ≥ 18 years;
3. Member meets one of the following (a or b):

a. Request is for the treatment of a member in a State with limitations on step therapy in certain mental health settings (*see Appendix E*);
b. For all other requests, all the following (i, ii, and iii):
   i. Failure of a ≥ 4-week trial of one selective serotonin reuptake inhibitor (SSRI) at up to maximally indicated doses unless contraindicated or clinically significant adverse effects are experienced;
   ii. Failure of two SNRIs at up to maximally indicated doses, each used for ≥ 4 weeks, unless clinically significant adverse effects are experienced or all are contraindicated;
   iii. Failure of a ≥ 4-week trial of another generic antidepressant (e.g., bupropion, TCA, mirtazapine, etc.) at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated;

4. Dose does not exceed both (a and b):
   a. 200 mg per day;
   b. 2 tablets per day.

Approval duration:
Medicaid/HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

C. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member is responding positively to therapy;

3. If request is for a dose increase, new dose does not exceed both (a and b):
   a. 200 mg per day;
   b. 2 tablets per day.

Approval duration:
Medicaid/HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration
MAOI: monoamine oxidase inhibitor
SNRI: selective serotonin and norepinephrine reuptake inhibitor
SSRI: selective serotonin reuptake inhibitor
TCA: tricyclic antidepressant

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
cyclobenzaprine (Flexeril®)	Fibromyalgia: 10 mg PO every morning and 20 mg at bedtime	30 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
bupropion (Wellbutrin®)	Depression: 100 mg PO three times daily	450 mg/day
bupropion SR (Wellbutrin SR®)	Depression: 150 mg PO twice daily	400 mg/day
bupropion XL (Wellbutrin XL®)	Depression: 150-450 mg PO once daily	450 mg/day
mirtazapine (Remeron®)	Depression: 15 mg PO once daily	45 mg/day
trazodone (Desyrel®)	Depression: 150mg PO in divided doses daily	400 mg/day
TCA		
amitriptyline (Elavil®)	Fibromyalgia: 10 mg to 50 mg PO once daily Depression: 50-100 mg PO daily	150 mg/day
doxepin (Sinequan®)	Depression: 75 mg PO daily	300 mg/day
imipramine (Tofranil®)	Depression: 75 mg PO daily	200 mg/day
nortriptyline (Pamelor®)	Depression: 75-100 mg PO either once daily or in divided doses Fibromyalgia: 25 mg to 50 mg PO once daily	150 mg/day
SSRIs		
citalopram (Celexa®)	Depression: 20-40 mg PO once daily	40 mg/day
escitalopram (Lexapro®)	Depression: 10 mg PO once daily	20 mg/day
fluoxetine (Prozac®)	Depression: 20 mg PO once daily	80 mg/day
fluvoxamine (Luvox®)	Depression (off-label): 50 mg PO once daily	300 mg/day
paroxetine (Paxil®)	Depression: 20 mg PO once daily	50 mg/day
paroxetine SR (Paxil CR®)	Depression: 25 mg PO once daily	62.5 mg/day
sertraline (Zoloft®)	Depression: 50 mg PO once daily	200 mg/day
SNRIs		
desvenlafaxine succinate (Pristiq®, Khedezla®)	Depression: 50 mg PO once daily	400 mg/day
duloxetine (Cymbalta®)	Fibromyalgia: 60 mg PO once daily Depression: 20 mg PO twice daily	60 mg/day
venlafaxine(Effexor®)	Depression:75 mg PO twice daily	375 mg/day
venlafaxine SR (Effexor XR®)	Depression: 37.5 mg PO once daily	225 mg/day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): concomitant use or use within 14 days of discontinuing a monoamine oxidase inhibitor (MAOI) used to treat psychiatric disorders, use of an MAOI within 5 days of discontinuing Savella, initiation of Savella in patients currently treated with linezolid or IV methylene blue due to increased risk of serotonin syndrome.

- Boxed warning(s): 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

Appendix D: General Information

- Class IIb recommendation in Micromedex for the treatment of depression.
- Use of MAOI with Savella concomitantly is contraindicated due to the risk of serious, sometimes, fatal, drug interactions with serotonergic drugs. These interactions have been associated with symptoms that include tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, rigidity, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Allow at least 14 days after stopping an MAOI before starting Savella. Allow at least 5 days after stopping Savella before starting an MAOI.
- Savella should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for 5 days or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with Savella may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue.
- Serotonin syndrome: Serotonin syndrome has been reported with SNRIs and SSRIs. Concomitant use of serotonergic drugs is not recommended.

Appendix E: States with Limitations against Redirections in Certain Mental Health Settings

State	Step Therapy Prohibited?	Notes
TX	No	**Applies to HIM requests only** **Depression**: Failure of ONE of the following at up to maximally indicated doses, each used for ≥ 4 weeks, unless clinically significant adverse effects are experienced or all are contraindicated: SSRI, SNRI, other generic antidepressants (e.g., bupropion, TCA, mirtazapine, etc.)

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Fibromyalgia	Based on efficacy and tolerability, PO dosing may 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) Recommended dose is 100 mg/day PO (50 mg twice daily)	200 mg/day (100 mg twice daily)
Depression (off-label)	Initially, 12.5 to 25 mg PO twice daily. Based on individual response, the dose may be titrated to 100 mg PO twice daily	200 mg/day (100 mg twice daily)

VI. Product Availability

Tablets: 12.5 mg, 25 mg, 50 mg, 100 mg

VII. References

1. Savella Prescribing Information. Irvine, CA: Allergan USA, Inc.; December 2022. Available at: https://www.savella.com/. Accessed February 5, 2023.
2. Clauw DJ. Fibromyalgia: a clinical review. JAMA. 2014; 311(15): 1547-1555.
3. Häuser W, Walitt B, Fitzcharles M-A, Sommer C. Review of pharmacological therapies in fibromyalgia syndrome. *Arthritis Research & Therapy*. 2014;16(1):201. doi:10.1186/ar4441.
4. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc. Updated periodically. Accessed February 5, 2023.
5. American Psychiatric Association: Practice guideline for the treatment of patients with major depressive disorder 3rd edition. Am J Psychiatry 2010;167(suppl):1-152.
6. Kia S, Choy E. Update on treatment guideline in fibromyalgia syndrome with focus on pharmacology. *Biomedicines*. 2017,5,20;doi:10.3990
7. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed February 5, 2023.
8. Heymann RE, Helfenstein M, Feldman D, et al. A double-blind, randomized, controlled study of amitriptyline, nortriptyline and placebo in patients with fibromyalgia. An analysis of outcome measures. Clin Exp Rheumatol. 2001;19(6)697-702.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
2Q 2019 annual review: no significant changes; added contraindications and boxed warnings; references reviewed and updated.	02.24.19	05.19
2Q 2020 annual review: revised criteria to allow trial of any TCA; allowed members 65 years old or older to bypass redirections to any TC and cyclobenzaprine; updated nortriptyline dose in appendix B; added depression (off-label) dose in section V; references reviewed and updated.	02.11.20	05.20
2Q 2021 annual review: no significant changes; references to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated.	01.11.21	05.21
Revised approval duration for Commercial line of business from length of benefit to 12 months or duration of request, whichever is less	09.28.21	02.22
2Q 2022 annual review: no significant changes; references reviewed and updated.	02.08.22	05.22
Template changes applied to other diagnoses/indications and continued therapy section.	10.03.22	
2Q 2023 annual review: shortened the trial durations of antidepressant agents from 8 weeks to 4 weeks; references reviewed and updated.	02.05.23	05.23
For depression, added redirection bypass for members in a State with limitations on step therapy in certain mental health settings along with	07.11.23	

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Appendix E, which includes Texas with requirements for single drug redirection for HIM requests; revised Appendix B therapeutic alternatives to organize by drug class.		

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.