Clinical Policy: Milnacipran (Savella)

Reference Number: ERX.NPA.65
Effective Date: 06.01.15
Last Review Date: 05.20
Line of Business: Commercial, 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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ 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 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 200 mg (2 tablets) per day.

Approval duration: 12 months

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

1. Diagnosis of depression;
2. Age ≥ 18 years;
3. Failure of a ≥ 8-week trial of one SSRI at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated;
4. Failure of two SNRIs at up to maximally indicated doses, each used for ≥ 8 weeks unless clinically significant adverse effects are experienced or all are contraindicated;
5. Failure of a ≥ 8-week trial of another generic antidepressant (e.g., bupropion, TCA, mirtazapine) at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated;
6. Dose does not exceed 200 mg (2 tablets) per day.

Approval duration: 12 months

C. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed 200 mg (2 tablets) per day.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 policy – ERX.PA.01 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

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 and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
amitriptyline (Elavil®)	Fibromyalgia: 10 mg to 50 mg PO once daily Depression: 75 mg PO daily	150 mg/day
nortriptyline (Pamelor®)	Fibromyalgia: 25 mg to 50 mg PO once daily	150 mg/day
cyclobenzaprine (Flexeril®)	Fibromyalgia: 10 mg PO every morning and 20 mg at bedtime	30 mg/day
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 -300 mg PO once daily	450 mg/day
citalopram (Celexa®)	Depression: 20-40 mg PO once daily	40 mg/day
desvenlafaxine succinate (Pristiq®)	Depression: 50 mg PO once daily	50 mg/day
doxepin (Sinequan®)	Depression: 75 mg PO daily	300 mg/day
duloxetine (Cymbalta®)	Fibromyalgia: 60 mg PO once daily	60 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
imipramine (Tofranil®)	Depression: 75 mg PO daily	200 mg/day
mirtazapine (Remeron®)	Depression: 15 mg PO once daily	45 mg/day
paroxetine (Paxil®)	Depression: 10 mg PO once daily	50 mg/day
paroxetine SR (Paxil CR®)	Depression: 12.5 mg PO once daily	62.5 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
sertraline (Zoloft®)	Depression: 50 mg PO once daily	200 mg/day
trazodone (Desyrel®)	Depression: 150 mg PO in divided doses daily	400 mg/day
venlafaxine(Effexor®)	Depression:75 mg PO once 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 an 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 depression.
- Use of monoamine oxidase inhibitors (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.

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 (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; December 2017. Available at: https://www.savella.com/. Accessed on February 11, 2020.
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.; 2020. Available at: http://www.clinicalpharmacology-ip.com/.
5. Kia S, Choy E. Update on treatment guideline in fibromyalgia syndrome with focus on pharmacology. Biomedicines. 2017,5,20;doi:10.3990
6. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed February 11, 2020.
7. 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
Policy created.	06.15	06.15
Updated to new template (converted algorithm to bulleted criteria, added background and references). Changed age restriction from ≥ 17 to ≥ 18 per FDA labeling ("Savella is not approved for use in pediatric patients"). Modified trial/failure requirement to include first-line options of amitriptyline and cyclobenzaprine per literature review.	07.16	09.16
Converted to new template. Added that trial of amitriptyline, cyclobenzaprine, or duloxetine should have occurred within the past 6 months. Modified generalized FDA max dose requirement to specific max dose of drug. Updated references.	06.17	08.17
2Q 2018 annual review: Converted policy from ST to clinical PA; Added off-label criteria for depression; Fibromyalgia: require failure of duloxetine, and if contraindicated a trial of amitriptyline or cyclobenzaprine; References reviewed and updated.	02.06.18	05.18
2Q 2019 annual review: no significant changes; references reviewed and updated.	02.25.19	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

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.

be bound by the foregoing terms and conditions, in addition to the Site Use Agreement for Health Plans associated with Envolve Pharmacy Solutions.