Clinical Policy: Milnacipran (Savella)

Reference Number: PA.CP.PMN.125
Effective Date: 10.17.18
Last Review Date: 04.17.19

Revision Log

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 PA Health & Wellness® 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. Member meets one of the following (a or b):
   a. Failure of a 30 day trial of duloxetine at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   b. If contraindication or intolerance to duloxetine, failure of a 30 day trial of amitriptyline or cyclobenzaprine at up to maximally indicated doses, unless both agents are contraindicated or clinically significant adverse effects are experienced;
3. Dose does not exceed 200 mg/day (2 tablets/day).

Approval duration: 12 months

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

1. Diagnosis of depression;
2. Failure of a ≥ 8 week trial of one SSRI at up to maximally indicated doses unless contraindicated or clinically significant adverse effects are experienced;
3. Failure of two SNRIs at up to maximally indicated doses, each used for ≥ 8 weeks unless contraindicated or clinically significant adverse effects are experienced;
4. Failure of a ≥ 8 week trial of another generic antidepressants (e.g., bupropion, TCA, mirtazapine, etc.) at up to maximally indicated doses unless contraindicated or clinically significant adverse effects are experienced;

5. Dose does not exceed 200 mg/day (2 tablets/day).

Approval duration: 12 months

C. Other diagnoses/indications

1. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53.

II. Continued Therapy

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

1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care Policy (PA.LTSS.PHAR.01) applies;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed 200 mg/day (2 tablets/day).

Approval duration: 12 months

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

1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care Policy (PA.LTSS.PHAR.01) applies.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53.

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 – PA.CP.PMN.53.

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 for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
amitriptyline (Elavil®)	Fibromyalgia: 10 mg to 50mg orally once daily	150 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
cyclobenzaprine (Flexeril®)	Fibromyalgia: 10mg every morning and 20 mg at bedtime	30 mg/day
bupropion (Wellbutrin®)	Depression: 100 mg orally 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
duloxetine (Cymbalta®)	Fibromyalgia: 60 mg PO once daily Depression: 20 mg PO 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
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
sertraline (Zoloft®)	Depression: 50 mg PO once daily	200 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
desvenlafaxine succinate (Pristiq®)	50 mg PO daily	50 mg/day
amitripytyline (Elavil®)	75 mg PO daily	150 mg/day
doxepin (Sinequan®)	75 mg PO daily	300 mg/day
imipramine (Tofranil®)	75 mg PO daily	200 mg/day
nortripytyline (Pamelor®)	50 mg PO daily	150 mg/day
trazodone (Desyrel®)	150mg PO in divided doses daily	400 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. Savella is not approved for use in pediatric patients.

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 PO (50 mg 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 2017. Available at: https://www.savella.com/. Accessed February 5, 2019.
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.; 2019. Available at: http://www.clinicalpharmacology-ip.com/.
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. Savella. ClinicalTrials.gov available at http://clinicaltrials.gov/ct2/show/study/NCT00797797. Accessed January 11, 2017.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy Created	10/18	
2Q 2019 annual review: added contraindications and boxed warnings; references reviewed and updated.	04/19	