RXADVANCE
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Clinical Policy Title:	milnacipran
Policy Number:	RxA.488
Drug(s) Applied:	Savella®
Original Policy Date:	03/06/2020
Last Review Date:	12/07/2020
Line of Business Policy Applies to:	All lines of business

Background

Milnacipran (Savella®) is a selective serotonin and norepinephrine reuptake inhibitor (SNRI). It is indicated for the management of fibromyalgia.

Limitation of use:
Savella® is not approved for use in pediatric patients.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
milnacipran (Savella®)	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)

Dosage Forms

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

Clinical Policy

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

I. Initial Approval Criteria

This clinical policy has been developed to authorize, modify, or determine coverage for individuals with similar conditions. Specific care and treatment may vary depending on individual need and benefits covered by the plan. This policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. This document may contain prescription brand name drugs that are trademarks of pharmaceutical manufacturers that are not affiliated with RxAdvance.

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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, 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 in the last 180 days, unless both agents are contraindicated or clinically significant adverse effects are experienced;
4. Dose does not exceed 200 mg/day.

Approval Duration
Commercial: 12 months
Medicaid: 12 months
HIM: 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 contraindicated or clinically significant adverse effects are experienced;
4. Failure of two SNRIs at up to maximally indicated doses, each used for ≥ 8 weeks unless contraindicated or clinically significant adverse effects are experienced;
5. Failure of a ≥ 8-week trial of another generic antidepressant (e.g., bupropion, TCA, mirtazapine, etc.) at up to maximally indicated doses unless contraindicated or clinically significant adverse effects are experienced;
6. Dose does not exceed 200 mg/day.

Approval duration
Commercial: 12 months
Medicaid: 12 months
HIM: 12 months

II. Continued Therapy

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

1. Currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed 200 mg/day.

Approval Duration
Commercial: 12 months
Medicaid: 12 months
HIM: 12 months

III. Appendices

Appendix A: Abbreviation/Acronym Key
MAOI: monoamine oxidase inhibitor
SNRI: selective serotonin and norepinephrine reuptake inhibitor
SSRI: selective serotonin reuptake inhibitor
TCA: tricyclic antidepressants

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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	Fibromyalgia: 10 mg to 50 mg PO once daily	150 mg/day
cyclobenzaprine	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
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	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	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

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Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
doxepin	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	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.

References

1. Savella® Prescribing Information. Irvine, CA: Allergan USA, Inc.; December 2017. Available at: www.savella.com. Accessed September 08, 2020.
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4. American Psychiatric Association: Practice guideline for the treatment of patients with major depressive disorder 3rd edition. Am J Psychiatry 2010;167(suppl):1-152. Accessed September 08, 2020.
5. Savella®. ClinicalTrials.gov available at http://clinicaltrials.gov/ct2/show/study/NCT00797797. Accessed

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7. Clinical Pharmacology [database online] powered by ClinicalKey. Tampa, FL: Elsevier, 2020. Accessed with subscription at: http://www.clinicalkey.com. Updated January 14, 2020. Accessed September 08, 2020.

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy was established	01/2020	03/06/2020
Policy was reviewed: 1. Policy title table was updated: Line of business policy applies was updated to All lines of business. 2. Continued therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance…". 3. Commercial approval duration was updated from Length of benefit to 12 months for Initial and continued approval criteria. 4. Appendix B was updated: discontinued preferred alternative brands were removed. 5. References were updated.	09/08/2020	12/07/2020

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