Clinical Policy: Milnacipran (Savella)

Reference Number: CP.PMN.125
Effective Date: 08.01.12 Revision Log
Last Review Date: 05.18
Line of Business: Commercial, HIM, Medicaid

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, unless contraindicated or clinically significant adverse effects are experienced;
   b. Contraindication or intolerance to duloxetine, and 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 (2 tablets/day).

Approval duration:
Medicaid/HIM - 12 months
Commercial - Length of Benefit

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 trialed for ≥ 8 weeks unless contraindicated or clinically significant adverse effects are experienced;
5. 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;
6. Dose does not exceed 200 mg/day (2 tablets/day).

Approval duration:
Medicaid/HIM - 12 months
Commercial - Length of Benefit

C. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

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

1. Currently receiving medication via Centene benefit 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/day (2 tablets/day).

Approval duration:
Medicaid/HIM - 12 months
Commercial - Length of Benefit

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

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 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.PHAR.21 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

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
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 orally twice daily	400 mg/day
bupropion XL (Wellbutrin XL®)	Depression: 150 -300 mg orally once daily	450 mg/day
citalopram (Celexa®)	Depression: 20-40 mg orally once daily	40 mg/day
desvenlafaxine succinate (Pristiq®)	Depression: 50 mg orally once daily	50 mg/day
duloxetine (Cymbalta®)	Fibromyalgia: 60 mg orally once daily Depression: 20 mg orally daily	60 mg/day
escitalopram (Lexapro®)	Depression: 10 mg orally once daily	20 mg/day
fluoxetine (Prozac®)	Depression: 20 mg orally once daily	80 mg/day
fluvoxamine (Luvox®)	Depression (off-label): 50 mg orally once daily	300 mg/day
mirtazapine (Remeron®)	Depression: 15 mg orally once daily	45 mg/day
paroxetine (Paxil®)	Depression: 10 mg orally once daily	50 mg/day
paroxetine SR (Paxil CR®)	Depression: 12.5 mg orally once daily	62.5 mg/day
sertraline (Zoloft®)	Depression: 50 mg orally once daily	200 mg/day
venlafaxine(Effexor®)	Depression:75 mg orally once daily	375 mg/day
venlafaxine SR (Effexor XR®)	Depression: 37.5 mg orally once daily	225 mg/day
desvenlafaxine succinate (Pristiq®)	50 mg orally daily	50 mg/day
amitripytyline (Elavil®)	75 mg orally daily	150 mg/day
doxepin (Sinequan®)	75 mg orally daily	300 mg/day
imipramine (Tofranil®)	75 mg orally daily	200 mg/day
nortripytyline (Pamelor®)	50 mg orally daily	150 mg/day
trazodone (Desyrel®)	150mg orally 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: General Information

- Class IIb recommendation in Micromedex for depression.
- Black box warning for Savella includes that these agents are not approved for use in pediatric patients. Pooled analyses of short-term placebo-controlled studies of antidepressant drugs (selective serotonin reuptake inhibitors (SSRIs) and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder and other psychiatric disorders.
- 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, 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)

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 January 10, 2018.
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.; 2017. 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
Updated criteria for trial and failure of medications prior to approval	08.14	08.14
Criteria modified to require use of first line trials for ≥ 30 days within the previous 6 months	08.15	08.15
Updated references to reflect current literature search Updated criteria for trial and failure to include cyclobenzaprine to criteria if contraindication to amitriptyline.; Added appropriate screening of drug to drug interaction of MAOI therapy due to absolute contraindication with Savella therapy; Updated Renewal Criteria to include member currently receiving medication through this health plan; Added max dose (200mg/day) to initial criteria #E and renewal criteria #B.	02.16	05.16
Modified criteria to allow trial and failure of either amitriptyline or cyclobenzaprine (instead of requiring trial of amitriptyline first prior to cyclobenzaprine) if duloxetine is contraindicated due to lack of evidence that one is better than the other; Converted to new template Modified age restriction from ≥ 17 years to ≥ 18 years-per PI, use of Savella is not recommended in pediatric population below the age of 18; Removed safety requirement related to "no concomitant use of monoamine oxidase inhibitors (MAOI) therapy OR history of MAOI therapy within the past 14 days" per template update; Added documentation of positive response to therapy for re-auth; Updated references	03.17	
2Q2018 annual review: polices combined for Medicaid, HIM, and Commercial lines of business; Medicaid & HIM: Added off-label criteria for depression; changed from trial of 2 antidepressants to trial of one SSRI, two SNRI and one other antidepressant; Commercial: Added failure of amitriptyline or cyclobenzaprine if duloxetine cannot be used; references reviewed and updated	02.06.18	05.18

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.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

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.

For Health Insurance Marketplace members, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the formulary exception policy.

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