



Original Effective Date: 04/2012
Current Effective Date: 03/13/2026
Last P&T Approval/Version: 01/28/2026
Next Review Due By: 01/2027
Policy Number: C4719-A

Serotonin - Norepinephrine Reuptake Inhibitors (SNRI)

PRODUCTS AFFECTED

desvenlafaxine tab ER, Fetzima (levomilnacipran), Pristiq (desvenlafaxine)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:

Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:

Major Depressive Disorder, Hot Flashes associated with Menopause

REQUIRED MEDICAL INFORMATION:

This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

Drug and Biologic Coverage Criteria

A. FOR ALL INDICATIONS:

1. Product being requested has an FDA labeled indication or compendia supported use for diagnosis, age, and dose
AND
2. Documentation of an adequate trial (3 months) and therapeutic failure to at least 3 formulary preferred SNRI products.
MOLINA REVIEWER NOTE: For Illinois Marketplace and Nevada Marketplace, please see Appendix.
AND
3. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Fetzima (levomilnacipran) include: Hypersensitivity to levomilnacipran, milnacipran HCl, or any excipient in the Fetzima formulation, do not use with MAOIs intended to treat psychiatric disorders or within 7 days of stopping treatment with Fetzima, do not use within 14 days of stopping an MAOI intended to treat psychiatric disorders, and do not start in patients being treated with linezolid or intravenous methylene blue. Contraindications to Pristiq (desvenlafaxine) include: Hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or any excipients in the Pristiq formulation, do not use with MAOIs intended to treat psychiatric disorders or within 7 days of stopping treatment with Pristiq, do not use within 14 days of stopping an MAOI intended to treat psychiatric disorders, and do not start in patients being treated with linezolid or intravenous methylene blue.]

CONTINUATION OF THERAPY:

A. FOR ALL INDICATIONS:

1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
AND
2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
AND
3. Documentation of positive clinical response as demonstrated by low disease activity and/or improvements in the condition's signs and symptoms

DURATION OF APPROVAL:

Initial authorization: 12 months, Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:

None

AGE RESTRICTIONS:

18 years of age and older

QUANTITY:

Fetzima: Maximum 120 mg once daily

Pristiq: 50 mg once daily, Maximum 100 mg once daily if moderate to severe hepatic impairment

PLACE OF ADMINISTRATION:

The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:

Oral

DRUG CLASS:

Serotonin – Norepinephrine reuptake inhibitors (SNRI)

FDA-APPROVED USES:

Indicated for the treatment of Major Depressive Disorder in adults

Limitations of Use (Fetzima only): Fetzima is not approved for the management of fibromyalgia. The efficacy and safety of Fetzima for the management of fibromyalgia have not been established.

COMPENDIAL APPROVED OFF-LABELED USES:

Treatment of Hot Flashes associated with Menopause (Pristiq)

APPENDIX

APPENDIX:

Reserved for State specific information. Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.

State Specific Information

State Marketplace

Illinois (Source: [Illinois General Assembly](#))

“(215 ILCS 134/45.1) Sec. 45.1. Medical exceptions procedures required. (c) An off-formulary exception request shall not be denied if: (1) the formulary prescription drug is contraindicated; (2) the patient has tried the formulary prescription drug while under the patient's current or previous health insurance or health benefit plan and the prescribing provider submits evidence of failure or intolerance; or (3) the patient is stable on a prescription drug selected by his or her health care provider for the medical condition under consideration while on a current or previous health insurance or health benefit plan. (d) Upon the granting of an exception request, the insurer, health plan, utilization review organization, or other entity shall authorize the coverage for the drug prescribed by the enrollee's treating health care provider, to the extent the prescribed drug is a covered drug under the policy or contract up to the quantity covered. (e) Any approval of a medical exception request made pursuant to this Section shall be honored for 12 months following the date of the approval or until renewal of the plan.”

Nevada (Source: [Nevada Legislature](#))

“Chapter 689A of Nevada Revised Statutes (NRS) is hereby amended by adding thereto a new section to read as follows:

1. A policy of health insurance which provides coverage for prescription drugs must not require an insured to submit to a step therapy protocol before covering a drug approved by the Food

Drug and Biologic Coverage Criteria

and Drug Administration that is prescribed to treat a psychiatric condition of the insured, if:

- a. The drug has been approved by the Food and Drug Administration with indications for the psychiatric condition of the insured or the use of the drug to treat that psychiatric condition is otherwise supported by medical or scientific evidence;
- b. The drug is prescribed by:
 - i. A psychiatrist
 - ii. A physician assistant under the supervision of a psychiatrist;
 - iii. An advanced practice registered nurse who has the psychiatric training and experience prescribed by the State Board of Nursing pursuant to NRS 632.120; or
 - iv. A primary care provider that is providing care to an insured in consultation with a practitioner listed in subparagraph (1), (2) or (3), if the closest practitioner listed in subparagraph (1), (2) or (3) who participates in the network plan of the insurer is located 60 miles or more from the residence of the insured; and
- c. The practitioner listed in paragraph (b) who prescribed the drug knows, based on the medical history of the insured, or reasonably expects each alternative drug that is required to be used earlier in the step therapy protocol to be ineffective at treating the psychiatric condition...

3. As used in this section:

- c. *‘Step therapy protocol’ means a procedure that requires an insured to use a prescription drug or sequence of prescription drugs other than a drug that a practitioner recommends for treatment of a psychiatric condition of the insured before his or her policy of health insurance provides coverage for the recommended drug.’*

Molina Reviewer Note: Medical necessity review for a psychiatric condition cannot require trial of other medications first. This is applicable to formulary medications that require prior authorization and non-formulary medications and is not limited to only medications designated ‘ST’. If the requested drug is a brand name and the generic is on formulary, request can be reviewed for specific medical reason generic cannot be used.

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Genetic Testing and Psychiatric Medication Choice

Pharmacogenomics is the study of the relationship between a genetic variation and how the body responds to medication. The American Psychiatric Association (APA) has a statement on pharmacogenomic testing based on results of their own task force looking at novel biomarkers and treatments. This task force determined “there is not sufficient information to support the widespread use of pharmacogenetic testing in clinical practice.” The 2020 International Society of Psychiatric Genetics (ISPG) guidelines on genetic testing states “Pharmacogenetic testing should be viewed as a decision-support tool to assist in thoughtful implementation of good clinical care. We recommend HLA-A and HLA-B testing prior to use of carbamazepine and oxcarbazepine, in alignment with regulatory agencies and expert groups. Evidence to support widespread use of other pharmacogenetic tests at this time is still inconclusive, but when pharmacogenetic testing results are already available, providers are encouraged to integrate this information into their medication selection and dosing decisions. Genetic information for CYP2C19 and CYP2D6 would likely be most beneficial for individuals who have experienced an inadequate response or adverse reaction to a previous antidepressant or antipsychotic trial.” The Pharmacogenomics Knowledgebase (PharmGKB) has summaries of genotype based *dosing* recommendations only,

Molina Healthcare, Inc. confidential and proprietary © 2026

This document contains confidential and proprietary information of Molina Healthcare and cannot be reproduced, distributed, or printed without written permission from Molina Healthcare. This page contains prescription brand name drugs that are trademarks or registered trademarks of pharmaceutical manufacturers that are not affiliated with Molina Healthcare.

Drug and Biologic Coverage Criteria

including the following:

- Aripiprazole: The Royal Dutch Pharmacists Association - Pharmacogenetics Working Group (DPWG) recommends reducing maximum dose of aripiprazole for patients carrying poor metabolizer alleles of CYP2D6.
- Antidepressants: The French National Network of Pharmacogenetics (Réseau national de pharmacogénétique (RNPGx)) recommends CYP2D6 and CYP2C19 genotyping before initiating an antidepressant treatment, especially in patients with a high risk of toxicity.
- Brexpiprazole: The Royal Dutch Pharmacists Association - Pharmacogenetics Working Group (DPWG) recommends to use half of the standard dose of brexpiprazole for patients carrying poor metabolizer alleles of CYP2D6.
- Duloxetine: There are currently no dosing recommendations for duloxetine based on CYP2D6 genotype.

At this time, there are no guidelines found that support the use of pharmacogenomic testing to make therapeutic treatment decisions based on the results of that testing. These tests may be beneficial to help guide dosing and toxicity concerns of specific agents for those with suboptimal responses or at risk of toxicity.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of SNRI's are considered experimental/investigational and therefore, will follow Molina's Off- Label policy.

Contraindications to Fetzima (levomilnacipran) include: Hypersensitivity to levomilnacipran, milnacipran HCl, or any excipient in the Fetzima formulation, do not use with MAOIs intended to treat psychiatric disorders or within 7 days of stopping treatment with Fetzima, do not use within 14 days of stopping an MAOI intended to treat psychiatric disorders, and do not start in patients being treated with linezolid or intravenous methylene blue.

Contraindications to Pristiq (desvenlafaxine) include: Hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or any excipients in the Pristiq formulation, do not use with MAOIs intended to treat psychiatric disorders or within 7 days of stopping treatment with Pristiq, do not use within 14 days of stopping an MAOI intended to treat psychiatric disorders, and do not start in patients being treated with linezolid or intravenous methylene blue.

OTHER SPECIAL CONSIDERATIONS:

Fetzima (levomilnacipran), and Pristiq (desvenlafaxine) have a Black Box Warning for suicidal thought and behaviors.

CODING/BILLING INFORMATION

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.

HCP CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:

Desvenlafaxine ER TB24 50MG, 100MG

Desvenlafaxine Succinate ER TB24 25MG, 50MG, 100MG

Fetzima CP24 20MG, 40MG, 80MG 120MG

Fetzima Titration C4PK 20 & 40MG

Pristiq TB24 25MG, 50MG, 100MG

REFERENCES

1. Fetzima (levomilnacipran) extended-release capsules, for oral use [prescribing information]. Madison, NJ: Allergan USA Inc; April 2024.
2. Khedezla (desvenlafaxine) [prescribing information]. Morristown, NJ: Pernix Therapeutics LLC; August 2023.
3. Pristiq (desvenlafaxine) Extended-Release Tablets, for oral use [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals LLC; June 2024.
4. Bauer M, Pfennig A, Severus E, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders, part 1: update 2013 on the acute and continuation treatment of unipolar depressive disorders. *World J Biol Psychiatry* 2013; 14:334.
5. Kupfer DJ, Frank E, Phillips ML. Major depressive disorder: new clinical, neurobiological, and treatment perspectives. *Lancet* 2012; 379:1045.
6. Marcus SC, Olfson M. National trends in the treatment for depression from 1998 to 2007. *Arch Gen Psychiatry* 2010; 67:1265.
7. News Author, Author, N., & APA Curated and updated for the community by APA. (2019, February 06). Genetic testing to improve psychiatric medication choice. Retrieved December 9, 2022, from <https://www.psychiatry.org/news-room/apa-blogs/genetic-testing-to-improve-psychiatric-medication>
8. Moran, M. (2018). Task Force on gene testing for antidepressant efficacy concludes tests not yet ready for widespread use. *Psychiatric News*, 53(14). doi:10.1176/appi.pn.2018.pp6b1
9. Zeier, Z., Carpenter, L. L., Kalin, N. H., Rodriguez, C. I., McDonald, W. M., Widge, A. S., & Nemeroff, C. B. (2018). Clinical implementation of Pharmacogenetic decision support tools for antidepressant drug prescribing. *American Journal of Psychiatry*, 175(9), 873-886. doi:10.1176/appi.ajp.2018.17111282
10. International Society of Psychiatric Genetics (ISPG) Genetic testing statement. (n.d.). Retrieved December 9, 2022, from <https://ispg.net/genetic-testing-statement/>
11. Pharmacogenomics Knowledgebase (PharmGKB) Clinical Guideline Annotations. (n.d.). Retrieved December 9, 2022, from <https://www.pharmgkb.org/guidelineAnnotations>
12. Gelenberg, A. J., & Freeman, M. P. (2010). Practice Guideline for the Treatment of Patients With Major Depressive Disorder, 3rd ed. *The Journal of Clinical Psychiatry*.
13. American Psychological Association. (2019). Clinical practice guideline for the treatment of depression across three age cohorts. Retrieved from <https://www.apa.org/depression-guideline>
14. Qaseem, A., Owens, D. K., Etzeandia-Ikobaltzeta, I., Tufte, J., Cross, J. T., & Wilt, T. J. (2023). Nonpharmacologic and pharmacologic treatments of adults in the acute phase of major depressive disorder: A living clinical guideline from the American College Of

SUMMARY OF REVIEW/REVISIONS	DATE
ANNUAL REVIEW COMPLETED- No coverage criteria changes with this annual review	Q1 2026
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Quantity Contraindications/Exclusions/Discontinuation Available Dosage Forms References	Q1 2025
REVISION- Notable revisions: FDA-Approved Uses Available Dosage Forms References	Q1 2024
REVISION- Notable revisions: Products Affected Diagnosis Required Medical Information Continuation of Therapy Quantity Compendial Approved Off-Labeled Uses Background Contraindications/Exclusions/Discontinuation Other Special Considerations Available Dosage Forms References	Q1 2023
Q2 2022 Established tracking in new format	Historical changes on file