Clinical Policy: Levomilnacipran (Fetzima)

Reference Number: HIM.PA.125
Effective Date: 12.01.17
Last Review Date: 08.26
Line of Business: HIM/ICHRA

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Levomilnacipran (Fetzima®) is a serotonin and norepinephrine reuptake inhibitor (SNRI).

FDA Approved Indication(s)

Fetzima is indicated for the treatment of major depressive disorder in adults.

Limitation(s) of use: Fetzima is not approved for the management of fibromyalgia. The efficacy and safety of Fetzima for the management of fibromyalgia have not been established.

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 Fetzima is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Major Depressive Disorder (must meet all)**:**

1. Diagnosis of major depressive disorder;
2. Age ≥ 18 years;
3. Member meets one of the following (a, b, or c):
   **For Illinois HIM requests, the step therapy requirements below do not apply per IL HB 5395*
   a. Request is for the treatment of a member in a State with limitations on step therapy in certain mental health settings (*see Appendix D*);
   b. Request is for Fidelis Ambetter (New York Exchange): Failure of ONE of the following, tried for ≥ 4 weeks at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated: selective serotonin reuptake inhibitor (SSRI), SNRI, bupropion, mirtazapine, vilazodone (generic Viibryd®);
   c. Failure of TWO antidepressants from at least two different drug classes, each tried for ≥ 4 weeks at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated: SSRI, SNRI, bupropion, mirtazapine, vilazodone (generic Viibryd®);
4. Dose does not exceed both of the following (a and b):
   a. 120 mg per day;
   b. 1 capsule per day.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: HIM.PA.33 for health insurance marketplace/ICHRA; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the non-formulary policy for the relevant line of business: HIM.PA.103 for health insurance marketplace/ICHRA; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: HIM.PA.154 for health insurance marketplace/ICHRA.

II. Continued Therapy

A. Major Depressive Disorder (must meet all)**:**
1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Fetzima for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed both of the following:
   a. 120 mg per day;
   b. 1 capsule per day.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: HIM.PA.33 for health insurance marketplace/ICHRA; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace/ICHRA) or PDL (Medicaid), the non-formulary policy for the relevant line of business: HIM.PA.103 for health insurance marketplace/ICHRA; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: HIM.PA.154 for health insurance marketplace/ICHRA.

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 –

HIM.PA.154 for health insurance marketplace/ICHRA, or evidence of coverage documents;

B. Fibromyalgia.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration
MAOI: monoamine oxidase inhibitor
SNRI: 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
bupropion (Wellbutrin® XL)	150-450 mg PO QAM	450 mg/day
bupropion (Wellbutrin SR)	150 mg PO QAM or 150-200 mg PO BID	400 mg/day
Aplenzin® (bupropion ER)	174 mg PO QAM	522 mg/day
mirtazapine (Remeron®)	15-45 mg PO QHS	45 mg/day
vilazodone (Viibryd)	10 mg PO QD for 7 days, followed by 20 mg PO QD	40 mg/day
SSRIs		
citalopram (Celexa®)	20 mg PO QD	40 mg/day
escitalopram (Lexapro®)	10-20 mg PO QD	20 mg/day
fluvoxamine†	50-300 mg PO QD	300 mg/day
fluoxetine (Prozac®)	20 mg PO QD	80 mg/day
fluoxetine delayed release (Prozac Weekly)	90 mg PO weekly	90 mg/ week
paroxetine (Paxil®)	20 mg PO QD	50 mg/day
paroxetine controlled release (Paxil CR®)	25 mg PO QD	62.5 mg/day
sertraline (Zoloft®)	50 mg PO QD	200 mg/day
SNRIs		
desvenlafaxine (Pristiq®)	50 mg PO QD	400 mg/day
duloxetine (Cymbalta®)	20-30 mg PO BID or 60 mg PO QD	60 mg/day
venlafaxine (Effexor® XR)	75 mg PO BID to TID	225 mg/day

†*Off-label*

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):
  - Hypersensitivity to levomilnacipran, milnacipran HCl, or any excipient;
  - Serotonin Syndrome and MAOIs: Do not use MAOIs intended to treat psychiatric disorders with Fetzima or within 7 days of stopping treatment with Fetzima. Do not use Fetzima within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start Fetzima in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue.
- Boxed warning(s): Increased risk of suicidal thoughts and behavior in pediatric and young adults taking antidepressants; closely monitor for clinical worsening and emergence of suicidal thoughts and behaviors; not approved for use in pediatric patients.

Appendix D: States with Limitations against Redirections in Certain Mental Health Settings

State	Step Therapy Prohibited?	Notes
TX	No	Failure of ONE of the following, used for ≥ 4 weeks at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated: SSRI, SNRI, bupropion, mirtazapine, vilazodone (generic Viibryd®)

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Major depressive disorder	40 mg-120 mg PO QD	120 mg/day

VI. Product Availability

Extended-release capsules: 20 mg, 40 mg, 80 mg, 120 mg

VII. References

1. Fetzima Prescribing Information. North Chicago, IL: AbbVie, Inc.; April 2024. Available at: www.fetzima.com. Accessed April 28, 2026.
2. Clinical Pharmacology [database online]. Tampa, FL: Elsevier.; 2026. URL: www.clinicalkeys.com/pharmacology. Accessed April 28, 2026.
3. Gelenberg AJ, Freeman MP, Markowitz JC, et al. Practice guideline for the treatment of patients with major depressive disorder, third edition. Arlington, VA: American Psychiatric Association; May 2010. Available online at: https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf . Accessed April 28, 2026.
4. McQuaid JR, Lin EH, Barber JP, et al. Clinical Practice Guideline for the Treatment of Depression across Three Age Cohorts. American Psychological Association, Adopted as APA Policy Feb. 16, 2019. Available at: https://www.apa.org/depression-guideline/guideline.pdf. Accessed April 28, 2026.
5. Qaseem A, Owens DK, Etxeandia-Ikobaltzeta I, et al. Nonpharmacologic and pharmacologic treatments of adults in the acute phase of major depressive disorder: a living clinical guideline from the American College of Physicians. *Ann Intern Med*. 2023 Feb;176(2):239-252. doi: 10.7326/M22-2056.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Template changes applied to other diagnoses/indications and continued therapy section.	10.11.22	
3Q 2023 annual review: added vilazodone (generic Viibryd) to list of redirect options; updated contraindications per prescribing information verbiage; added redirection bypass for members in a State with limitations on step therapy in certain mental health settings along with Appendix E, which includes Texas with requirements for single drug redirection for HIM requests; references reviewed and updated.	04.18.23	08.23
Per SDC, revised to allow single step redirection for Fidelis Ambetter (New York Exchange).	01.18.24	
3Q 2024 annual review: revised continued therapy to allow continuity of care for antidepressants; in Appendix B, added Wellbutrin SR to therapeutic alternatives and clarified that fluvoxamine used in depression is off-label; references reviewed and updated.	05.29.24	08.24
3Q 2025 annual review: clarified failure of two antidepressants from at least two different drug classes; added step therapy bypass for IL HIM per IL HB 5395; in Appendix B, updated therapeutic alternatives per Clinical Pharmacology; references reviewed and updated.	05.08.25	08.25
3Q 2026 annual review: added ICHRA line of business; removed "applies to HIM request only" from Appendix D for TX; references reviewed and updated.	04.28.26	08.26

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.