SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITOR

Levomilnacipran

Fetzima

The most noradrenergic SNRI, useful when fatigue and low motivation dominate, but limited by tachycardia and urinary retention.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
40-120 mg/day PO	12 h	CYP3A4; 58% renal unchanged	1-2 wks; 6-8 wks full

⚠ FDA BOXED WARNING

Suicidal thoughts and behaviors: antidepressants increased the risk of suicidality in pediatric and young adult patients in short-term studies. Closely monitor all treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. Not approved for use in pediatric patients.

INDICATIONS

- FDA-approved only for major depressive disorder in adults, at **40-120 mg once daily** after a brief 20 mg lead-in.
- Not approved for any anxiety, pain, or pediatric indication, which distinguishes it sharply from duloxetine and venlafaxine.
- Its enantiomer milnacipran is approved in the United States for fibromyalgia, but levomilnacipran itself has no pain indication.
- Often selected off-label when fatigue, apathy, and impaired concentration dominate the depressive presentation.
- Fixed-dose trials showed benefit at 40, 80, and 120 mg/day, with the number needed to treat for response near 8 to 10.
- Not a first-line agent in major guidelines, given its cost, cardiovascular effects, and lack of comparative advantage over SSRIs.

DOSING & TITRATION

- Start **20 mg** PO once daily for two days, then increase to **40 mg once daily**, which is the minimum effective dose.
- Titrate by 40 mg increments at intervals of at least two days; the effective range is 40 to 120 mg/day and the maximum is **120 mg/day**.
- Reduce the maximum to **80 mg/day** in moderate renal impairment and to 40 mg/day in severe impairment; avoid in end-stage renal disease.
- Cap the dose at 80 mg/day when a strong CYP3A4 inhibitor such as ketoconazole, clarithromycin, or ritonavir is co-prescribed.
- Supplied as 20, 40, 80, and 120 mg extended-release capsules that must be swallowed whole, not opened, chewed, or crushed.
- Taper gradually rather than stopping abruptly, since the 12 hour half-life makes discontinuation symptoms likely.

MECHANISM OF ACTION

- Inhibits both monoamine transporters but with roughly twofold greater potency at the norepinephrine transporter than at the serotonin transporter.
- That reversed selectivity is unique among marketed SNRIs, all of which are otherwise more serotonergic than noradrenergic.
- Predominant noradrenergic action is the rationale for its use in depression marked by low energy, apathy, and poor concentration.
- The same noradrenergic tone produces the heart rate rise, hypertension, hyperhidrosis, and urinary hesitancy seen in trials.
- It is the active levo-enantiomer of milnacipran and has no meaningful muscarinic, histaminic, or adrenergic receptor blockade.

PHARMACOKINETICS

- Absolute bioavailability is about 92 percent and is unaffected by food, so the extended-release capsule may be taken with or without meals.
- Half-life is approximately **12 hours**, with once-daily extended-release dosing and steady state reached in two to three days.
- Roughly **58 percent** of a dose is excreted unchanged in urine, which is why renal function drives the maximum permitted dose.
- Hepatic metabolism proceeds mainly through CYP3A4, with minor contributions from CYP2C8, 2C19, 2D6, and 2J2 and no active metabolites.
- It does not meaningfully inhibit or induce CYP enzymes, so it rarely alters the concentration of co-prescribed medications.

ADVERSE EFFECTS

- Nausea occurs in about 17 percent of patients, with constipation, vomiting, and decreased appetite also common early in treatment.
- Heart rate rises by roughly **7 beats per minute** on average, and palpitations or tachycardia are among the more frequent complaints.
- Blood pressure increases modestly and dose-dependently, so uncontrolled hypertension should be corrected before initiation.
- Urinary hesitancy and retention are more common than with other SNRIs and reflect the drug's noradrenergic dominance.
- Erectile dysfunction, ejaculatory disorder, and hyperhidrosis are frequent and often lead patients to request a switch.
- Serotonin syndrome, hyponatremia, mydriasis with angle-closure risk, and increased bleeding are the serious prescribing concerns.

MONITORING

- Measure heart rate and blood pressure at baseline, after each dose increase, and periodically during maintenance treatment.
- Estimate creatinine clearance before starting, since renal function sets the dose ceiling and end-stage disease precludes use.
- Ask specifically about urinary hesitancy and incomplete emptying, particularly in men with benign prostatic hyperplasia.
- Assess suicidality, activation, and agitation weekly for the first four weeks and after each dose change, especially under age 25.
- Track response with the PHQ-9 or MADRS every two to four weeks and reassess if there is no change by week six at 80 mg/day.

INTERACTIONS & CAUTIONS

- Contraindicated with MAOIs and within **14 days** of stopping one, and with linezolid or intravenous methylene blue.
- Strong CYP3A4 inhibitors raise exposure and require the dose to be capped at **80 mg/day** for as long as they are co-prescribed.
- Strong CYP3A4 inducers such as carbamazepine, rifampin, and phenytoin can reduce concentrations and cause apparent nonresponse.
- Additive noradrenergic effects with stimulants, atomoxetine, and decongestants can produce clinically significant tachycardia.
- Additive serotonin syndrome risk with triptans, tramadol, fentanyl, and lithium, and additive bleeding risk with NSAIDs and anticoagulants.

SPECIAL POPULATIONS

- Pregnancy data are very limited, so a better-characterized antidepressant should generally be chosen when treatment is needed in gestation.
- Lactation data are essentially absent; if breastfeeding, choose an agent with an established infant safety record instead.
- Not approved for pediatric use, and no adequate controlled trials in children or adolescents have been published.
- In older adults titrate cautiously and monitor heart rate, blood pressure, urinary retention, and hyponatremia more closely.
- Renal impairment governs dosing: **80 mg/day** maximum at moderate impairment, 40 mg/day at severe, and avoid in end-stage disease.

PRESCRIBING PEARLS

- The only SNRI that is more noradrenergic than serotonergic, so think energy, focus, and blood pressure.
- Ask men about urinary hesitancy before and after starting; retention is the distinguishing side effect.
- Renal function sets the ceiling: 80 mg/day if moderate impairment, 40 mg/day if severe.

Verify against the current FDA label and your formulary before prescribing. Educational reference only.

References

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NOTE

References follow APA 7th edition style. Dosing, boxed warnings, and interaction data change; confirm every clinical decision against the current FDA prescribing information (DailyMed) and your institution's formulary. This sheet is an educational quick reference and does not replace the full label or clinical judgment.