SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITOR

Desvenlafaxine

Pristiq, Khedezla

The active metabolite of venlafaxine, given at one flat 50 mg dose with minimal CYP involvement and no titration required.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
50 mg/day PO	11 h	UGT conjugation; minor CYP3A4	1-2 wks; 6-8 wks full

⚠ FDA BOXED WARNING

Suicidal thoughts and behaviors: antidepressants increased the risk in children, adolescents, and young adults in short-term studies, with no increase after age 24 and reduced risk at 65 and older. Monitor all patients closely for clinical worsening and emergent suicidality. Not approved in pediatric patients.

INDICATIONS

- FDA-approved only for major depressive disorder in adults, at a recommended dose of **50 mg once daily** with or without food.
- Fixed-dose trials found no added antidepressant benefit above 50 mg/day, only more nausea, sweating, and treatment discontinuation.
- Off-label for generalized anxiety disorder and other anxiety conditions, extrapolating from venlafaxine rather than from its own trials.
- Off-label at **50-100 mg/day** for vasomotor symptoms of menopause, an indication supported by several randomized trials.
- Off-label for neuropathic pain and fibromyalgia, where duloxetine and milnacipran hold the actual approvals and stronger evidence.
- Sometimes chosen when a patient is a CYP2D6 poor metabolizer or takes multiple interacting drugs, since it bypasses that enzyme.

DOSING & TITRATION

- The recommended dose is **50 mg** PO once daily; no titration is needed and most patients never require a higher dose.
- Doses of 100, 200, and 400 mg/day were studied without added efficacy, so escalation should be reserved for clear partial response.
- In moderate renal impairment the maximum is **50 mg/day**, and in severe impairment or end-stage renal disease it is 50 mg every other day.
- In moderate to severe hepatic impairment the maximum recommended dose is **100 mg/day**, and escalation above 50 mg should be cautious.
- Supplied as 25, 50, and 100 mg extended-release tablets that must be swallowed whole; the inert shell may be visible in stool.
- Taper gradually when stopping, and use the 25 mg tablet for the final steps, since abrupt cessation produces venlafaxine-like withdrawal.

MECHANISM OF ACTION

- Inhibits both the serotonin and norepinephrine transporters, with a serotonin-to-norepinephrine potency ratio of roughly ten to one.
- Unlike venlafaxine, it delivers noradrenergic activity at the standard **50 mg/day** dose without requiring dose escalation.
- Increased noradrenergic tone contributes to improvements in energy and concentration and to sweating and blood pressure elevation.
- It is the O-desmethyl metabolite of venlafaxine, so the two drugs share a pharmacologic profile and should never be combined.
- No meaningful muscarinic, histaminic, or alpha-adrenergic receptor blockade, so weight and sedation effects are limited.

PHARMACOKINETICS

- Absolute bioavailability is about 80 percent and is unaffected by food, so administration timing can follow patient preference.
- Half-life is approximately **11 hours**, sufficient for once-daily extended-release dosing with steady state in four to five days.
- Metabolized primarily by UGT-mediated conjugation with only a minor CYP3A4 oxidative pathway, so CYP interactions are few.
- About **45 percent** of a dose is excreted unchanged in urine, which is why renal impairment mandates explicit dose limits.
- It is not a clinically important inhibitor of CYP2D6 at 50 mg/day, though weak inhibition emerges at 100 mg/day and above.

ADVERSE EFFECTS

- Nausea occurs in roughly 22 percent at 50 mg/day, usually in the first two weeks, along with dry mouth, headache, and dizziness.
- Sweating and hyperhidrosis are noradrenergically mediated, dose-related, and among the most persistent complaints over time.
- Sexual dysfunction rates rise with dose and include reduced libido, delayed ejaculation, and erectile difficulty in a minority of patients.
- Blood pressure and heart rate increase modestly and dose-dependently, so uncontrolled hypertension should be treated before starting.
- Discontinuation syndrome, hyponatremia, mydriasis with angle-closure risk, and increased bleeding are the serious prescribing issues.
- Elevated fasting cholesterol and triglycerides were seen in longer-term trials, more often at doses above 100 mg/day.

MONITORING

- Measure blood pressure at baseline, at two to four weeks, and periodically thereafter, particularly if the dose exceeds 50 mg/day.
- Assess suicidality, activation, and agitation weekly for the first four weeks and after any dose change, especially under age 25.
- Check creatinine and estimate clearance at baseline, since renal function directly determines the maximum permitted dose.
- Obtain a fasting lipid panel at baseline and annually, or sooner in patients maintained above 100 mg/day.
- Check serum sodium at baseline and within two to four weeks in older adults, diuretic users, or anyone with new confusion.

INTERACTIONS & CAUTIONS

- Contraindicated with MAOIs and within **14 days** of stopping one, and with linezolid or intravenous methylene blue.
- Should never be combined with venlafaxine, since desvenlafaxine is its active metabolite and the effects are simply additive.
- Additive serotonin syndrome risk with triptans, tramadol, fentanyl, lithium, tryptophan, and St. John's wort.
- Additive hypertensive and tachycardic effects with stimulants and with other noradrenergic agents such as atomoxetine.
- Increases bleeding risk with aspirin, NSAIDs, warfarin, and direct oral anticoagulants through impaired platelet serotonin uptake.

SPECIAL POPULATIONS

- Pregnancy data are more limited than for the SSRIs; late-gestation exposure carries neonatal adaptation and pulmonary hypertension risk.
- Breast milk data are sparse, with a relative infant dose estimated near 6 percent, so infant monitoring is advised if used.
- Not approved in pediatric patients, and adolescent depression trials did not demonstrate separation from placebo.
- In older adults start at **50 mg/day** and check renal function first, since falls, hyponatremia, and hypertension risks all increase.
- Renal impairment is the key adjustment: **50 mg/day** maximum if clearance is 30 to 50 mL/min, and every other day below 30 mL/min.

PRESCRIBING PEARLS

- One flat 50 mg dose works for most patients; higher doses add side effects without adding efficacy.
- Bypasses CYP2D6 entirely, which is its main advantage over venlafaxine on complex regimens.
- Renal function sets the ceiling: 50 mg every other day when clearance falls below 30 mL/min.

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.