SEROTONIN MODULATOR

Vilazodone

Viibryd

Combined serotonin reuptake inhibitor and 5-HT1A partial agonist for adult depression, requiring food with every dose and a slow three-step titration.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
20-40 mg/day PO with food	25 h	CYP3A4 major; 2C19, 2D6 minor	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, with a target dose of **20 or 40 mg once daily** taken with food.
- Not approved for any pediatric indication; a large adolescent depression trial failed to separate from placebo on the primary outcome.
- Off-label for generalized anxiety disorder, where two phase III trials showed benefit at 20 and 40 mg/day but did not yield an approval.
- Sometimes chosen off-label when sexual dysfunction has limited SSRI tolerability, though head-to-head superiority remains unproven.
- A reasonable off-label option for anxious depression given the anxiolytic contribution of its 5-HT1A partial agonism.
- Not a first-line agent in most guidelines because of cost, gastrointestinal burden, and the absence of comparative efficacy advantage.

DOSING & TITRATION

- Start **10 mg** PO once daily with food for seven days, increase to **20 mg/day** for seven days, then to 40 mg/day if needed.
- The effective range is **20 to 40 mg/day**, and the label maximum is 40 mg/day; skipping the titration steps sharply increases nausea and diarrhea.
- Cap the dose at **20 mg/day** when a strong CYP3A4 inhibitor such as ketoconazole, clarithromycin, or ritonavir is co-prescribed.
- With a strong CYP3A4 inducer used for more than 14 days, the dose may be doubled over one to two weeks, not exceeding 80 mg/day.
- Available as 10, 20, and 40 mg tablets and a 10 mg plus 20 mg starter pack designed to enforce the stepwise titration.
- No adjustment is needed for renal impairment or for mild to moderate hepatic impairment; taper gradually rather than stopping abruptly.

MECHANISM OF ACTION

- Blocks the serotonin transporter with SSRI-like potency while simultaneously acting as a partial agonist at postsynaptic and somatodendritic 5-HT1A receptors.
- The 5-HT1A partial agonism mimics buspirone augmentation and is intended to shorten the delay to raphe autoreceptor desensitization.
- That dual action theoretically buffers the early anxiety and sexual side effects that follow pure transporter blockade.
- Has no meaningful affinity for norepinephrine or dopamine transporters, or for muscarinic, histaminic, and adrenergic receptors.
- Clinical trials have not demonstrated a faster onset or lower sexual dysfunction rate than SSRIs despite the mechanistic rationale.

PHARMACOKINETICS

- Bioavailability is about 72 percent when taken with food and falls by roughly 50 percent when fasting, so every dose must accompany a meal.
- Half-life is approximately **25 hours**, giving once-daily dosing with steady state reached after about three days at a stable dose.
- Metabolized principally by CYP3A4 with minor contributions from CYP2C19 and CYP2D6, and it produces no clinically active metabolites.
- Strong CYP3A4 inhibitors roughly double exposure, while strong inducers used beyond two weeks can cut concentrations by about half.
- It is 96 to 99 percent protein bound and eliminated mostly in feces, with less than 2 percent excreted unchanged in urine.

ADVERSE EFFECTS

- Diarrhea occurs in roughly **28 percent** of patients and nausea in about 23 percent, making gastrointestinal upset the dominant tolerability issue.
- Taking each dose with a substantial meal and titrating slowly are the two interventions that most reliably reduce those symptoms.
- Insomnia, dizziness, dry mouth, and abnormal dreams are common, and vomiting occurs more often than with standard SSRIs.
- Sexual dysfunction rates in trials were low but the comparisons were placebo-controlled, not against an active SSRI comparator.
- Serotonin syndrome, hyponatremia, activation of mania, and increased bleeding risk with NSAIDs or anticoagulants apply as with any SSRI.
- Weight change is minimal in short-term trials, averaging under 1 kg over eight weeks of treatment.

MONITORING

- Confirm at each visit that the patient is taking every dose with food, since fasting administration halves exposure and mimics nonresponse.
- Assess suicidality, activation, and agitation weekly for the first four weeks and after each dose increase, especially under age 25.
- Track response with the PHQ-9 or MADRS every two to four weeks and allow six to eight weeks at 40 mg/day before declaring failure.
- Check serum sodium at baseline and within two to four weeks in older adults or patients taking diuretics.
- Review the medication list for strong CYP3A4 inhibitors or inducers at initiation and whenever any new prescription is added.

INTERACTIONS & CAUTIONS

- Contraindicated with MAOIs and within **14 days** of stopping one, and with linezolid or intravenous methylene blue.
- Strong CYP3A4 inhibitors including ketoconazole, clarithromycin, and ritonavir require the dose to be reduced to **20 mg/day**.
- Strong CYP3A4 inducers such as carbamazepine, rifampin, phenytoin, and St. John's wort can halve exposure and cause apparent nonresponse.
- Additive serotonin syndrome risk with triptans, tramadol, fentanyl, lithium, and other serotonergic antidepressants.
- Increases bleeding risk in combination with aspirin, NSAIDs, warfarin, and direct oral anticoagulants.

SPECIAL POPULATIONS

- Pregnancy data are limited, so better-characterized agents such as sertraline are preferred when treatment is needed during gestation.
- Lactation data are essentially absent; if a serotonergic agent is required while nursing, choose one with an established infant safety record.
- Not approved in pediatrics, and the adolescent depression program failed to demonstrate efficacy over placebo.
- No dose adjustment is required by age, but older adults are more susceptible to hyponatremia, falls, and gastrointestinal fluid loss.
- No adjustment is needed in renal impairment or in mild to moderate hepatic impairment; severe hepatic impairment has not been studied.

PRESCRIBING PEARLS

- Always with food. Fasting cuts absorption by half and looks exactly like treatment failure.
- Diarrhea and nausea drive dropouts; the 10-20-40 mg stepwise titration exists to limit them.
- Add a 5-HT1A partial agonist to an SSRI and you have the same idea for far less money.

References

AbbVie. (2024). *Viibryd (vilazodone hydrochloride) [Prescribing information]*. U.S. Food and Drug Administration. https://dailymed.nlm.nih.gov/dailymed/

Cipriani, A., Furukawa, T. A., Salanti, G., Chaimani, A., Atkinson, L. Z., Ogawa, Y., Leucht, S., Ruhe, H. G., Turner, E. H., Higgins, J. P. T., Egger, M., Takeshima, N., Hayasaka, Y., Imai, H., Shinohara, K., Tajika, A., Ioannidis, J. P. A., & Geddes, J. R. (2018). Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: A systematic review and network meta-analysis. *The Lancet*, *391*(10128), 1357-1366. https://doi.org/10.1016/S0140-6736(17)32802-7

Kennedy, S. H., Lam, R. W., McIntyre, R. S., Tourjman, S. V., Bhat, V., Blier, P., Hasnain, M., Jollant, F., Levitt, A. J., MacQueen, G. M., McInerney, S. J., McIntosh, D., Milev, R. V., Muller, D. J., Parikh, S. V., Pearson, N. L., Ravindran, A. V., & Uher, R. (2016). Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 3. Pharmacological treatments. *The Canadian Journal of Psychiatry*, *61*(9), 540-560. https://doi.org/10.1177/0706743716659417

Khan, A., Cutler, A. J., Kajdasz, D. K., Gallipoli, S., Athanasiou, M., Robinson, D. S., Whalen, H., & Reed, C. R. (2011). A randomized, double-blind, placebo-controlled, 8-week study of vilazodone, a serotonergic agent for the treatment of major depressive disorder. *The Journal of Clinical Psychiatry*, *72*(4), 441-447. https://doi.org/10.4088/JCP.10m06596

National Institute for Health and Care Excellence. (2022). *Depression in adults: Treatment and management* (NICE Guideline No. 222). https://www.nice.org.uk/guidance/ng222

National Library of Medicine. (2024). *Vilazodone*. MedlinePlus. https://medlineplus.gov/druginfo/meds/a611020.html

Stahl, S. M. (2021). *Stahl's essential psychopharmacology: Neuroscientific basis and practical applications* (5th ed.). Cambridge University Press.

U.S. Department of Veterans Affairs & U.S. Department of Defense. (2022). *VA/DoD clinical practice guideline for the management of major depressive disorder*. https://www.healthquality.va.gov/guidelines/MH/mdd/

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.