SECOND-GENERATION ANTIPSYCHOTIC

Iloperidone

Fanapt

Low-akathisia antipsychotic whose price is a mandatory slow titration for orthostasis and dose-related QT prolongation.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
12-24 mg/day PO divided BID	18-33 h by CYP2D6 status	CYP2D6, CYP3A4	Slow; 1-2 wk titration

⚠ FDA BOXED WARNING

Increased mortality in elderly patients with dementia-related psychosis treated with antipsychotic drugs; iloperidone is not approved for the treatment of patients with dementia-related psychosis.

INDICATIONS

- Schizophrenia in adults, for acute treatment and for maintenance, with efficacy comparable to other second-generation agents at adequate doses.
- Acute manic or mixed episodes associated with bipolar I disorder in adults, an indication added to the label in 2024.
- Often selected for patients who cannot tolerate akathisia or parkinsonism on aripiprazole, risperidone, or lurasidone.
- Useful when prolactin elevation has been the limiting problem, since iloperidone raises prolactin only modestly.
- Off-label use is limited, largely to patients whose main constraint is movement side effects rather than efficacy.

DOSING & TITRATION

- Start **1 mg twice daily** and double the twice-daily dose on each of days 2 through 4, reaching 6 mg twice daily by day 4.
- Continue to **8 mg twice daily** on day 5, 10 mg twice daily on day 6, and 12 mg twice daily on day 7 if tolerated.
- The effective range is **12-24 mg/day** given in two divided doses, and the labeled maximum is **24 mg/day**.
- Halve the dose with strong **CYP2D6** inhibitors such as fluoxetine or paroxetine, with strong CYP3A4 inhibitors, and in known poor metabolizers.
- Restart the full titration from 1 mg twice daily whenever the drug has been stopped for more than **3 days**.
- Avoid in severe hepatic impairment, and taper gradually on discontinuation to avoid rebound symptoms.

MECHANISM OF ACTION

- Antagonist at dopamine **D2** and **D3** receptors with high **5-HT2A** affinity, giving a favorable ratio that limits extrapyramidal effects.
- Very potent alpha-1 adrenergic blockade is the source of the orthostatic hypotension and dizziness that dictate the titration schedule.
- Low histamine H1 and negligible muscarinic affinity mean modest sedation and no anticholinergic burden.
- Blockade of cardiac potassium channels underlies a dose-related QTc prolongation of roughly 9 ms at the higher end of dosing.
- Low striatal D2 occupancy at therapeutic doses accounts for the notably low rates of akathisia and parkinsonism seen in trials.

PHARMACOKINETICS

- Oral absorption is unaffected by food and peak concentrations occur 2-4 hours after dosing, with twice-daily administration required.
- Metabolized by **CYP2D6** and **CYP3A4** to two active metabolites, P88 and P95, which contribute meaningfully to overall effect.
- Half-life is about **18 hours** in CYP2D6 extensive metabolizers and about **33 hours** in poor metabolizers, who need half the usual dose.
- Steady state takes 3-4 days after each dose step, which is why the labeled titration is spread across a full week.
- Renal clearance of unchanged drug is minimal, but severe hepatic impairment is a reason to avoid the drug altogether.

ADVERSE EFFECTS

- Dizziness and orthostatic hypotension are the leading effects and are the entire reason for the slow, stepwise titration.
- Tachycardia, somnolence, dry mouth, nasal congestion, and fatigue are common, with nasal congestion reflecting alpha-1 blockade.
- QTc prolongation is dose related, averaging about **9 ms** at 12 mg twice daily, and rises further with metabolic inhibitors.
- Weight gain is intermediate, averaging **2-3 kg**, with modest effects on lipids and fasting glucose.
- Akathisia and extrapyramidal symptoms are among the lowest in the class, and prolactin elevation is small.
- Neuroleptic malignant syndrome, tardive dyskinesia, and priapism are rare but serious labeled risks.

MONITORING

- Baseline and follow-up ECG when there is cardiac disease, bradycardia, electrolyte disturbance, or concurrent QT-prolonging medication.
- Correct hypokalemia and hypomagnesemia before starting, and recheck electrolytes when diuretics or vomiting enter the picture.
- Orthostatic blood pressure and pulse at each step of the titration and after any interruption that requires restarting.
- Weight, BMI, fasting glucose or A1c, and lipids at baseline, 12 weeks, and annually, as for all antipsychotics.
- Ask about CYP2D6 inhibitor use at every visit, since adding fluoxetine or paroxetine effectively doubles the dose.

INTERACTIONS & CAUTIONS

- Strong **CYP2D6** inhibitors including fluoxetine, paroxetine, and bupropion roughly double exposure and require halving the dose.
- Strong **CYP3A4** inhibitors such as ketoconazole, clarithromycin, and ritonavir likewise call for a **50 percent** dose reduction.
- Strong inducers such as rifampin and carbamazepine markedly reduce exposure and combination is not recommended.
- Avoid combining with other QT-prolonging drugs including Class IA and III antiarrhythmics, methadone, and moxifloxacin.
- Additive orthostasis with antihypertensives and additive sedation with opioids, benzodiazepines, and alcohol.

SPECIAL POPULATIONS

- Third-trimester exposure carries the class risk of neonatal extrapyramidal and withdrawal signs; human pregnancy data are limited.
- Lactation data are essentially absent, so prefer better-characterized agents or monitor the infant closely for sedation.
- Safety and effectiveness have not been established in pediatric patients, so use is confined to adults.
- In older adults the orthostatic burden and fall risk are substantial, and the dementia mortality warning applies.
- No renal adjustment is specified, but the drug is not recommended in severe hepatic impairment.

PRESCRIBING PEARLS

- The week-long titration is not optional; skipping it produces syncope, not faster response.
- Off the drug more than 3 days means restarting at 1 mg twice daily and titrating again.
- Consider it when akathisia has repeatedly ended treatment with other agents.

References

Huhn, M., Nikolakopoulou, A., Schneider-Thoma, J., Krause, M., Samara, M., Peter, N., Arndt, T., Backers, L., Rothe, P., Cipriani, A., Davis, J., Salanti, G., & Leucht, S. (2019). Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: A systematic review and network meta-analysis. *The Lancet, 394*(10202), 939-951. https://doi.org/10.1016/S0140-6736(19)31135-3

National Institute for Health and Care Excellence. (2014). *Psychosis and schizophrenia in adults: Prevention and management* (Clinical guideline CG178). https://www.nice.org.uk/guidance/cg178

National Institute of Diabetes and Digestive and Kidney Diseases. (2023). Iloperidone. In *LiverTox: Clinical and research information on drug-induced liver injury*. National Library of Medicine. https://www.ncbi.nlm.nih.gov/books/NBK548669/

Pillinger, T., McCutcheon, R. A., Vano, L., Mizuno, Y., Arumuham, A., Hindley, G., Beck, K., Natesan, S., Efthimiou, O., Cipriani, A., & Howes, O. D. (2020). Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: A systematic review and network meta-analysis. *The Lancet Psychiatry, 7*(1), 64-77. https://doi.org/10.1016/S2215-0366(19)30416-X

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

Vanda Pharmaceuticals Inc. (2026). *FANAPT (iloperidone) tablets [Prescribing information]*. U.S. Food and Drug Administration. https://dailymed.nlm.nih.gov/dailymed/

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.