

Pimavanserin

Nuplazid

Selective 5-HT_{2A} inverse agonist with no dopamine blockade, approved only for hallucinations and delusions in Parkinson disease psychosis.

USUAL ADULT RANGE

34 mg/day PO

HALF-LIFE

57 h (metabolite ~200 h)

METABOLISM

CYP3A4 and CYP3A5

ONSET

Delayed; 4-6 wks

FDA BOXED WARNING

Increased mortality in elderly patients with dementia-related psychosis treated with antipsychotic drugs; pimavanserin is not approved for patients with dementia-related psychosis unless the hallucinations and delusions are related to Parkinson's disease psychosis.

INDICATIONS

- Hallucinations and delusions associated with Parkinson's disease psychosis in adults, which is its only approved indication.
- Chosen precisely because it does not block dopamine receptors and therefore does not worsen motor function in Parkinson disease.
- Guidelines position it alongside low-dose quetiapine and clozapine after reducing dopaminergic medication and treating reversible causes.
- Off-label use in dementia-related psychosis without Parkinson disease is not supported and runs directly into the boxed warning.
- Off-label interest in Lewy body dementia psychosis exists, but trial results have been mixed and the drug is not approved for it.

DOSING & TITRATION

- The recommended dose is **34 mg once daily** as a single capsule or as two 17 mg tablets, with no titration required.
- Reduce to **10 mg once daily** when a strong CYP3A4 inhibitor such as ketoconazole or itraconazole is used concomitantly.
- Avoid strong **CYP3A4** inducers including rifampin, carbamazepine, phenytoin, and St. John's wort, since exposure falls substantially.
- Before starting, reduce or simplify dopaminergic therapy where possible and treat delirium, infection, and metabolic causes of psychosis.
- Allow at least **4-6 weeks** at full dose before judging response, since the long half-life delays maximal effect.
- No adjustment is needed for mild to moderate renal impairment, and no formal taper schedule is specified.

MECHANISM OF ACTION

- Selective inverse agonist and antagonist at serotonin **5-HT_{2A}** receptors, with lesser activity at 5-HT_{2C} and none at 5-HT_{2B}.
- It has no measurable affinity for dopamine **D₂** receptors, which is why motor symptoms of Parkinson disease do not worsen.
- No meaningful muscarinic, histaminergic, or adrenergic binding, so there is little sedation, orthostasis, or anticholinergic effect.
- The 5-HT_{2A} hypothesis of Parkinson disease psychosis holds that visual hallucinations arise from cortical serotonergic dysregulation.
- Because the mechanism is purely serotonergic, it does nothing for the positive symptoms of primary schizophrenia.

PHARMACOKINETICS

- Bioavailability is about 80 percent and absorption is not clinically affected by food, so it can be taken at any consistent time.
- Metabolized principally by **CYP3A4** and CYP3A5 to the active metabolite AC-279, with CYP2J2 and CYP2D6 playing minor roles.
- Half-life is about **57 hours** for parent drug and roughly 200 hours for the active metabolite, so steady state takes about 12 days.
- The long half-life explains both the delayed onset of benefit and the persistence of adverse effects after stopping.
- Not recommended in severe renal impairment with creatinine clearance under **30 mL/min** or in hepatic impairment.

ADVERSE EFFECTS

- Peripheral edema occurs in about **7 percent** and confusion or a confusional state in about 6 percent, both more than with placebo.
- Nausea, constipation, gait disturbance, and hallucination are the other commonly reported treatment-emergent effects.
- QTc prolongation averages **5-8 ms**, which matters mainly when other QT-prolonging drugs are already in use.
- Older patients with dementia show increased mortality and serious adverse events, which is the substance of the boxed warning.
- Because there is no dopamine blockade, extrapyramidal worsening, prolactin elevation, and metabolic changes are not expected.

MONITORING

- Baseline ECG in patients with cardiac disease, bradycardia, electrolyte disturbance, or concurrent QT-prolonging medication.
- Assess cognition and confusion at follow-up, since worsening confusion is a common reason to stop the drug in this population.
- Check for new or worsening peripheral edema, particularly in patients with heart failure or venous insufficiency.
- Reassess benefit at 6 weeks and periodically thereafter, and discontinue if hallucinations and delusions have not improved.
- Review renal and hepatic function before starting, since both severe renal and any hepatic impairment make the drug unsuitable.

INTERACTIONS & CAUTIONS

- Strong **CYP3A4** inhibitors such as ketoconazole, itraconazole, clarithromycin, and ritonavir require reducing the dose to 10 mg daily.
- Strong **CYP3A4** inducers markedly reduce exposure and concomitant use should be avoided rather than compensated with a higher dose.
- Avoid combining with Class IA and III antiarrhythmics, methadone, moxifloxacin, and other drugs that prolong the QT interval.
- Additive confusion and anticholinergic burden when combined with amantadine, trihexyphenidyl, or other anticholinergic Parkinson agents.
- There is no contraindication other than hypersensitivity, and pimavanserin does not antagonize levodopa or dopamine agonists.

SPECIAL POPULATIONS

- Pregnancy and lactation data are essentially absent, which is of limited practical relevance in the typical Parkinson disease population.
- Safety and effectiveness have not been established in pediatric patients and there is no plausible pediatric indication.
- The trial population was elderly with Parkinson disease, so geriatric use is the norm, but dementia-related psychosis alone is excluded.
- Not recommended when creatinine clearance falls below 30 mL/min, since exposure rises without a defined reduced dose.
- Hepatic impairment has not been studied and use is not recommended in patients with significant liver disease.

PRESCRIBING PEARLS

- No dopamine blockade, so it is the one antipsychotic that will not worsen parkinsonism.
- Allow 4-6 weeks before judging response; the metabolite half-life is roughly 200 hours.
- It has no role in schizophrenia or in dementia psychosis outside Parkinson disease.

References

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

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.