

Paliperidone

Invega, Invega Sustenna, Invega Trinza, Invega Hafyera

Active metabolite of risperidone with minimal CYP metabolism and the deepest long-acting injectable line, from monthly to every 6 months.

USUAL ADULT RANGE

3-12 mg/day PO; 6 mg typical

HALF-LIFE

23 h oral; 25-49 d LAI

METABOLISM

Minimal CYP; 59% renal

ONSET

1-2 wks; 4-6 wks full

FDA BOXED WARNING

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

INDICATIONS

- Schizophrenia in adults and in adolescents ages 12-17 with the oral extended-release tablet, and in adults with the injectable formulations.
- Schizoaffective disorder in adults as monotherapy or as an adjunct to mood stabilizers or antidepressants, an indication unique in this class.
- Invega Sustenna is given monthly for schizophrenia and schizoaffective disorder, including after an inadequate response to oral treatment.
- Invega Trinza is given every 3 months only after at least 4 months of adequately dosed monthly Sustenna treatment.
- Invega Hafyera is given every 6 months after at least 4 months of Sustenna or one cycle of Trinza, the longest interval available in psychiatry.

DOSING & TITRATION

- Oral schizophrenia and schizoaffective disorder: **6 mg once daily** in the morning, with a usual range of 3-12 mg/day and no titration required.
- Adolescents under 51 kg have a maximum of **6 mg/day** and those at or above 51 kg a maximum of **12 mg/day**.
- Invega Sustenna initiation is **234 mg IM** in the deltoid on day 1 and **156 mg IM** on day 8, then 39-234 mg monthly in deltoid or gluteal muscle.
- Invega Trinza is 3.5 times the stabilized monthly dose, giving **273-819 mg IM every 3 months**, and Hafyera is 1092 or 1560 mg every 6 months.
- Renal dose caps: maximum **6 mg/day** oral when creatinine clearance is 50-79 mL/min and 3 mg/day when 10-49 mL/min; avoid below 10 mL/min.
- Injectables are not recommended when creatinine clearance is under **50 mL/min**, and mild impairment requires a reduced initiation regimen.

MECHANISM OF ACTION

- Paliperidone is 9-hydroxyrisperidone, the active metabolite of risperidone, so its receptor profile is essentially that of its parent drug.
- Potent antagonism at dopamine **D2** and serotonin **5-HT2A** receptors provides antipsychotic efficacy with dose-related extrapyramidal risk.
- Alpha-1 and alpha-2 adrenergic blockade produces orthostatic hypotension and reflex tachycardia, most evident during oral titration.
- Tuberoinfundibular D2 blockade raises prolactin more than any other agent in the class, a frequent reason for switching.
- Histamine H1 affinity is moderate, giving some sedation and appetite effect but less than olanzapine or quetiapine.

PHARMACOKINETICS

- The oral tablet uses an osmotic push-pull system giving about 28 percent bioavailability and a flat concentration curve over 24 hours.
- Metabolism is minimal, with roughly **59 percent** excreted unchanged in urine, so CYP-mediated drug interactions are largely avoided.
- Oral half-life is about **23 hours**; the injectable forms have apparent half-lives of 25-49 days and take months to reach steady state.
- Food increases oral exposure, so instruct patients to take the tablet the same way each day, either always with or always without breakfast.
- Renal clearance dominates, so exposure rises sharply as creatinine clearance falls and dose caps apply below **80 mL/min**.

ADVERSE EFFECTS

- Hyperprolactinemia is the most characteristic effect, producing amenorrhea, galactorrhea, gynecomastia, and sexual dysfunction.
- Dose-related extrapyramidal symptoms including akathisia, parkinsonism, and dystonia become common above **6 mg/day** oral equivalent.
- Tachycardia, orthostatic hypotension, and dizziness occur early, and injection-site pain and induration are common with the injectables.
- Weight gain is moderate, generally intermediate in the class, with modest effects on lipids and fasting glucose.
- Tardive dyskinesia, neuroleptic malignant syndrome, and rare gastrointestinal obstruction with the nondeformable oral shell are the serious risks.

MONITORING

- Baseline and periodic weight, BMI, blood pressure, fasting glucose or A1c, and lipids, at 12 weeks and then annually.
- Serum creatinine and estimated creatinine clearance before starting and periodically, because dosing is entirely renally driven.
- Prolactin level whenever menstrual change, galactorrhea, gynecomastia, or sexual dysfunction is reported, and consider bone density if prolonged.
- AIMS at baseline and every 6-12 months, with closer attention in older patients and at higher dose equivalents.
- For injectables, confirm the correct needle length and injection site and document the interval, since a missed window requires a reinitiation algorithm.

INTERACTIONS & CAUTIONS

- Because metabolism is minimal, CYP interactions are few, which makes paliperidone attractive in patients on complex medication regimens.
- Strong inducers such as **carbamazepine** and rifampin still reduce exposure by about 35 percent through P-glycoprotein and mixed pathways.
- Additive orthostatic hypotension with antihypertensives and additive sedation with opioids, benzodiazepines, and alcohol.
- Additive QT effect with Class IA and III antiarrhythmics, methadone, and macrolides, though intrinsic QT risk is modest.
- Paliperidone antagonizes levodopa and dopamine agonists, so avoid it in Parkinson disease psychosis.

SPECIAL POPULATIONS

- Third-trimester exposure risks neonatal extrapyramidal and withdrawal symptoms, and long-acting forms cannot be withdrawn quickly if needed.
- Lactation data are limited but modeled infant exposure is low; monitor breastfed infants for sedation and feeding problems.
- Oral use is approved from age 12 for schizophrenia, with weight-based dose caps and greater prolactin sensitivity than in adults.
- In older adults dose by renal function rather than age alone, and start at **3 mg/day** oral when clearance is reduced.
- No specific adjustment is needed in mild to moderate hepatic impairment; severe impairment has not been studied.

PRESCRIBING PEARLS

- Choose paliperidone over risperidone when CYP2D6 interactions or variable metabolism are the problem.
- Dose is set by creatinine clearance, so recheck renal function before every dose increase.
- Trinza and Hafyera require prior stabilization on Sustenna; they are not starting formulations.

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](https://doi.org/10.1016/S0140-6736(19)31135-3)
- Janssen Pharmaceuticals, Inc. (2026). *INVEGA (paliperidone) extended-release tablets [Prescribing information]*. U.S. Food and Drug Administration. <https://dailymed.nlm.nih.gov/dailymed/>
- Leucht, S., Cipriani, A., Spineli, L., Mavridis, D., Orey, D., Richter, F., Samara, M., Barbui, C., Engel, R. R., Geddes, J. R., Kissling, W., Stapf, M. P., Lassig, B., Salanti, G., & Davis, J. M. (2013). Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: A multiple-treatments meta-analysis. *The Lancet*, 382(9896), 951-962. [https://doi.org/10.1016/S0140-6736\(13\)60733-3](https://doi.org/10.1016/S0140-6736(13)60733-3)
- 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). Paliperidone. In *LiverTox: Clinical and research information on drug-induced liver injury*. National Library of Medicine. <https://www.ncbi.nlm.nih.gov/books/NBK548506/>
- 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.