FIRST-GENERATION ANTIPSYCHOTIC

Fluphenazine

Prolixin, Prolixin Decanoate (brands discontinued; generic only)

High-potency phenothiazine available as tablets, elixir, and a decanoate depot for long-term maintenance of chronic psychotic illness.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
2.5-20 mg/day PO; max 40 mg	~15 h PO; ~14 d decanoate	CYP2D6; hepatic	1-2 wks; decanoate 24-72 h

⚠ FDA BOXED WARNING

Increased mortality in elderly patients with dementia-related psychosis treated with antipsychotic drugs; fluphenazine is not approved for dementia-related psychosis.

INDICATIONS

- FDA-approved for the management of manifestations of psychotic disorders in adults, principally schizophrenia and schizoaffective disorder.
- The decanoate depot is FDA-approved for patients who require prolonged parenteral antipsychotic therapy, including those with poor oral adherence.
- Off-label use in acute mania and in psychotic depression as an adjunct, though second-generation agents now hold the guideline recommendations.
- Off-label control of severe chronic tics and Tourette syndrome when higher-potency dopamine blockade is needed and pimozide is unsuitable.
- Off-label management of chorea and behavioral dyscontrol in Huntington disease, generally after VMAT2 inhibitors have been considered.
- Not indicated for dementia-related psychosis, delirium prophylaxis, or nonpsychotic anxiety, where risk clearly exceeds benefit.

DOSING & TITRATION

- Oral therapy starts at **2.5-10 mg/day** divided every 6 to 8 hours; most patients stabilize on a maintenance dose of **1-5 mg/day**.
- Increase gradually by 2.5 mg steps; doses above **20 mg/day** are rarely more effective and the labeled ceiling is **40 mg/day**.
- Decanoate is usually initiated at **12.5-25 mg** intramuscularly or subcutaneously every 2 to 3 weeks, adjusted in 12.5 mg increments.
- A common conversion is a decanoate dose in milligrams roughly equal to 1.2 times the stabilized oral daily dose given every 2 weeks.
- No renal adjustment is defined; reduce doses and extend intervals in hepatic impairment because clearance is entirely hepatic.
- Taper oral therapy over weeks; when stopping a depot, remember drug persists for 6 to 8 weeks after the final injection.

MECHANISM OF ACTION

- High-affinity postsynaptic dopamine D2 antagonism in the mesolimbic pathway underlies antipsychotic efficacy at low milligram doses.
- Nigrostriatal D2 blockade at the same doses gives one of the highest extrapyramidal symptom rates among available antipsychotics.
- Tuberoinfundibular blockade produces marked, sustained hyperprolactinemia with amenorrhea, galactorrhea, and reduced bone mineral density.
- Weak muscarinic and histaminic affinity means less sedation and dry mouth than chlorpromazine but no intrinsic protection against dystonia.
- Modest alpha-1 antagonism gives intermediate orthostatic risk, and 5-HT2A blockade is minor compared with second-generation agents.

PHARMACOKINETICS

- Oral bioavailability is low and variable at roughly 20-50 percent because of substantial first-pass hepatic metabolism.
- The hydrochloride salt has a half-life near 15 hours, while the decanoate ester behaves as a depot with an apparent half-life of about 14 days.
- Decanoate is hydrolyzed in muscle to free fluphenazine, peaking at 24-72 hours and reaching steady state after roughly 4 to 6 injections.
- CYP2D6 is the principal metabolizing enzyme, so poor metabolizers and patients on 2D6 inhibitors accumulate drug and extrapyramidal effects.
- Protein binding exceeds 90 percent and the drug is highly lipophilic, with negligible renal elimination of unchanged fluphenazine.

ADVERSE EFFECTS

- Extrapyramidal symptoms dominate, with akathisia, parkinsonism, and acute dystonia reported in a third or more of treated patients.
- Tardive dyskinesia risk is high with chronic exposure, on the order of 5 percent per year in adults and considerably more in older patients.
- Hyperprolactinemia is nearly universal at therapeutic doses, causing menstrual disruption, galactorrhea, and sexual dysfunction.
- Neuroleptic malignant syndrome, though rare, is well described with high-potency phenothiazines and can occur weeks after a depot injection.
- Sedation, orthostatic hypotension, and anticholinergic effects are milder than with chlorpromazine but still limit dosing in frail patients.
- Rare but serious effects include agranulocytosis, cholestatic jaundice, QT prolongation, seizures, and photosensitivity reactions.

MONITORING

- Baseline and semiannual AIMS assessment, with a directed extrapyramidal exam at every visit during titration and after each depot change.
- Baseline CBC and liver enzymes, repeated if fever, sore throat, jaundice, or unexplained malaise develops during therapy.
- ECG at baseline in patients with cardiac disease, electrolyte disturbance, or concurrent QT-prolonging drugs, and after dose escalation.
- Prolactin level when amenorrhea, galactorrhea, or sexual dysfunction appears, with bone density review for long-term elevated levels.
- Weight, fasting glucose, and lipids at baseline and annually, plus creatine kinase whenever rigidity or unexplained fever emerges.

INTERACTIONS & CAUTIONS

- CYP2D6 inhibitors such as fluoxetine, paroxetine, bupropion, and duloxetine raise fluphenazine levels and markedly increase extrapyramidal risk.
- Enzyme inducers including carbamazepine, phenytoin, and rifampin lower concentrations and can cause loss of psychotic symptom control.
- Additive QT prolongation with methadone, ondansetron, macrolides, and class III antiarrhythmics; correct hypokalemia before combining.
- Additive sedation and respiratory depression with opioids, benzodiazepines, and alcohol, and additive hypotension with antihypertensives.
- Contraindicated in comatose states, severe CNS depression, subcortical brain damage, blood dyscrasias, liver disease, and phenothiazine allergy.

SPECIAL POPULATIONS

- Pregnancy exposure lacks a clear teratogenic signal, but third-trimester use risks neonatal extrapyramidal signs and withdrawal symptoms.
- Fluphenazine passes into breast milk in small amounts; monitor the infant for sedation and abnormal movements if nursing continues.
- Safety and efficacy in children have not been established, so pediatric use is off-label and should be reserved for specialist settings.
- In older adults start at the lowest effective dose given heightened tardive dyskinesia risk and the boxed dementia mortality warning.
- Hepatic impairment is a labeled contraindication in significant liver disease; renal impairment requires no specific dose adjustment.

PRESCRIBING PEARLS

- Depot drug lingers 6-8 weeks after the last dose, so new movement problems can start late.
- Test tolerability with oral fluphenazine before committing a patient to the decanoate depot.
- Prophylactic benztropine is often needed given the very high acute dystonia rate in young men.

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.