FIRST-GENERATION ANTIPSYCHOTIC

Loxapine

Loxitane, Adasuve

Dibenzoxazepine antipsychotic with atypical-like serotonin blockade; the inhaled form treats agitation within ten minutes under a REMS.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
60-100 mg/day PO; max 250 mg	**~6-8 h; active metabolites**	**CYP1A2, 2D6, 3A4; hepatic**	**Inhaled 10 min; PO 1-2 wks**

⚠ FDA BOXED WARNING

Increased mortality in elderly patients with dementia-related psychosis. The inhalation powder (Adasuve) can cause bronchospasm leading to respiratory distress and respiratory arrest, so it is restricted to REMS-certified sites with airway management capability.

INDICATIONS

- Oral loxapine is FDA-approved for the treatment of schizophrenia in adults, given in divided doses after gradual titration.
- Inhaled loxapine is FDA-approved for acute agitation associated with schizophrenia or bipolar I disorder in adults, limited to one dose per day.
- The inhaled product is dispensed only through a restricted REMS program at healthcare facilities equipped for advanced airway management.
- Off-label oral use for acute agitation and for augmentation in partially responsive psychosis when a different receptor profile is wanted.
- Off-label low-dose use has been described for anxiety and for migraine, but evidence is thin and the boxed warning still applies.
- Not indicated for dementia-related psychosis, and inhaled loxapine is contraindicated in any patient with active airway disease.

DOSING & TITRATION

- Start oral loxapine at **10 mg** twice daily; severe presentations may begin at **50 mg/day** in divided doses under close observation.
- Titrate over 7 to 10 days to a usual maintenance range of **60-100 mg/day** divided two to four times daily; the labeled maximum is **250 mg/day**.
- Inhaled loxapine is a single **10 mg** oral inhalation, not to be repeated within 24 hours, with the patient observed for bronchospasm.
- Before each inhaled dose, screen for asthma, COPD, or other lung disease, and examine the chest for wheezing; those conditions are contraindications.
- No formal renal or hepatic dose adjustment exists, but lower doses and slower titration are prudent when clearance is likely reduced.
- Taper oral therapy over weeks; abrupt discontinuation risks cholinergic rebound, insomnia, nausea, and withdrawal dyskinesias.

MECHANISM OF ACTION

- Blocks dopamine D2 receptors with mid-range potency, providing antipsychotic efficacy at total daily doses of roughly 60 to 100 milligrams.
- Substantial 5-HT2A antagonism gives a serotonin-to-dopamine ratio resembling second-generation agents, which may soften extrapyramidal effects at low doses.
- The metabolite 7-hydroxyloxapine is a potent D2 blocker, while 8-hydroxyloxapine contributes little, shaping the overall clinical response.
- Loxapine is structurally related to amoxapine, and small amounts of that antidepressant metabolite give weak norepinephrine reuptake inhibition.
- Moderate histamine H1, muscarinic, and alpha-1 blockade account for sedation, dry mouth, and orthostatic hypotension during titration.

PHARMACOKINETICS

- Oral absorption is rapid but bioavailability is limited by first-pass metabolism, with peak plasma concentrations reached in 1 to 2 hours.
- Inhaled loxapine reaches peak plasma levels in about 2 minutes, which explains the calming effect within 10 minutes of a single dose.
- The plasma half-life is roughly 6 to 8 hours for the parent drug, with hydroxylated metabolites persisting substantially longer.
- Metabolism proceeds through CYP1A2, CYP2D6, and CYP3A4 plus glucuronidation, so smoking and 2D6 inhibitors both shift exposure meaningfully.
- Elimination is mainly biliary and renal as conjugated metabolites, with negligible unchanged loxapine recovered in the urine.

ADVERSE EFFECTS

- Sedation is the most common effect of both formulations, and dizziness with orthostatic hypotension is frequent during oral titration.
- Extrapyramidal symptoms including akathisia and parkinsonism occur in a dose-dependent fashion, generally less than with haloperidol.
- Bronchospasm is the defining risk of the inhaled product and can progress to respiratory distress or arrest in patients with airway disease.
- Dysgeusia and throat irritation affect a substantial minority after inhalation, and are usually transient and self-limited.
- Tardive dyskinesia, neuroleptic malignant syndrome, and hyperprolactinemia occur as class effects with sustained oral treatment.
- Loxapine lowers seizure threshold appreciably, so use caution in patients with epilepsy, withdrawal states, or head injury.

MONITORING

- Before any inhaled dose, take a respiratory history and auscultate the chest; monitor for wheeze and dyspnea every 15 minutes for at least 1 hour.
- Keep a short-acting bronchodilator and advanced airway equipment immediately available wherever inhaled loxapine is administered.
- Perform baseline and semiannual AIMS testing plus an extrapyramidal exam at each visit for patients on continuing oral therapy.
- Check orthostatic blood pressure during oral titration, and obtain an ECG when cardiac disease or other QT-prolonging agents are present.
- Weight, fasting glucose, and lipids at baseline and annually, with CBC and liver enzymes if symptoms suggest dyscrasia or hepatic injury.

INTERACTIONS & CAUTIONS

- CYP1A2 inducers such as tobacco smoke and CYP3A4 inducers such as carbamazepine reduce loxapine exposure and may cause symptom breakthrough.
- CYP2D6 and CYP1A2 inhibitors including fluvoxamine, paroxetine, and ciprofloxacin raise levels and increase sedation and movement effects.
- Additive CNS and respiratory depression with opioids, benzodiazepines, and alcohol, which is especially hazardous with the inhaled route.
- Additive anticholinergic and hypotensive effects with antihistamines, tricyclics, and antihypertensives; combined QT drugs merit ECG review.
- Inhaled loxapine is contraindicated in asthma, COPD, other bronchospastic lung disease, and in patients with acute wheezing on examination.

SPECIAL POPULATIONS

- Pregnancy data are limited; third-trimester exposure carries the class risk of neonatal extrapyramidal symptoms and withdrawal.
- Loxapine and its metabolites appear in breast milk, so nursing infants should be observed for sedation and feeding difficulty.
- Safety and efficacy in patients under 18 have not been established for either the oral or the inhaled formulation.
- Older adults are more sensitive to sedation and hypotension, and the boxed dementia mortality warning limits use in that group.
- No formal renal or hepatic dosing guidance exists; start low and titrate slowly when either organ system is compromised.

☆ PRESCRIBING PEARLS

- Inhaled loxapine calms agitation in about 10 minutes but needs a REMS site and an hour of watching.
- Its 5-HT2A blockade makes low-dose loxapine behave more like an atypical than a classic typical agent.
- Ask about asthma and listen to the lungs before every single inhaled dose, not just the first.

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.