SECOND-GENERATION ANTIPSYCHOTIC

Asenapine

Saphris, Secuado

Sublingual-only antipsychotic with a broad receptor profile; oral numbness and twice-daily dosing are the usual limits.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
5-10 mg SL twice daily	About 24 h	UGT1A4, CYP1A2	1-2 wks; 4-6 wks full

⚠ FDA BOXED WARNING

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

INDICATIONS

- Schizophrenia in adults, for acute treatment and for maintenance, using the sublingual tablet or the Secuado transdermal patch.
- Acute manic or mixed episodes of bipolar I disorder in adults as monotherapy or as adjunct to lithium or valproate.
- Acute manic or mixed episodes of bipolar I disorder in pediatric patients ages 10-17 as monotherapy, with a slower titration schedule.
- Secuado is a once-daily transdermal system approved only for schizophrenia in adults, useful when sublingual dosing is not tolerated.
- Off-label use includes patients who cannot swallow tablets reliably or where covert nonadherence to oral therapy is suspected.

DOSING & TITRATION

- Schizophrenia in adults: **5 mg sublingually twice daily**, which may be increased to 10 mg twice daily after one week if needed.
- Bipolar mania monotherapy in adults: start **10 mg sublingually twice daily** and reduce to 5 mg twice daily if tolerability is a problem.
- As adjunct to lithium or valproate, start at **5 mg twice daily** and increase to 10 mg twice daily based on response and tolerability.
- Pediatric bipolar mania ages 10-17: start **2.5 mg twice daily**, increase to 5 mg twice daily after 3 days, then to 10 mg twice daily after 3 more.
- Secuado transdermal is **3.8 mg per 24 hours**, increased to 5.7 or 7.6 mg per 24 hours after at least one week, applied to intact skin.
- Contraindicated in severe hepatic impairment; no adjustment is required for renal impairment, and taper gradually when stopping.

MECHANISM OF ACTION

- High-affinity antagonist across dopamine **D2**, **D3**, and D4 receptors and multiple serotonin receptors, giving an unusually broad profile.
- Very potent **5-HT2A**, 5-HT2C, 5-HT6, and 5-HT7 antagonism may contribute to effects on mood, negative symptoms, and cognition.
- Alpha-1 and alpha-2 adrenergic blockade produces orthostatic hypotension and dizziness, especially during the first week.
- Histamine H1 affinity is high and drives sedation and appetite, while muscarinic affinity is negligible so anticholinergic effects are minimal.
- Local anesthetic action on the oral mucosa explains the oral hypoesthesia and altered taste that patients report immediately after dosing.

PHARMACOKINETICS

- Sublingual bioavailability is about **35 percent**, but falls below 2 percent if the tablet is swallowed, so route counts as part of the dose.
- Patients must not eat or drink for **10 minutes** after dosing, since water within that window markedly reduces absorption.
- Cleared by direct **UGT1A4** glucuronidation and by **CYP1A2** oxidation, with asenapine itself a moderate CYP2D6 inhibitor.
- Terminal half-life is about **24 hours** but twice-daily dosing is required because of the mucosal absorption profile.
- Exposure rises about sevenfold in severe hepatic impairment, which makes Child-Pugh class C an outright contraindication.

ADVERSE EFFECTS

- Oral hypoesthesia, tongue numbness, and altered taste occur in about **5-25 percent** and are the most common reason patients stop the drug.
- Somnolence, dizziness, and akathisia are common and dose related, with akathisia more frequent at 10 mg twice daily than at 5 mg.
- Weight gain is intermediate, generally less than olanzapine or quetiapine but more than lurasidone or ziprasidone.
- Extrapyramidal symptoms and modest prolactin elevation occur, and oral ulceration or blistering has been reported at the application site.
- Serious hypersensitivity including anaphylaxis, angioedema, and hypotension is specifically labeled and can occur after the first dose.

MONITORING

- Weight, BMI, blood pressure, fasting glucose or A1c, and lipids at baseline, at 12 weeks, and annually thereafter.
- Inspect the oral mucosa at follow-up visits for ulceration, blistering, or persistent numbness that would justify switching to the patch.
- Assess orthostatic vital signs during the first week, particularly in older adults and in patients on antihypertensives.
- AIMS examination at baseline and every 6-12 months, with specific attention to akathisia at each visit in the first month.
- Check liver function before starting, since severe hepatic impairment contraindicates the drug entirely.

INTERACTIONS & CAUTIONS

- Asenapine is a moderate **CYP2D6** inhibitor and can roughly double paroxetine exposure, so reduce the paroxetine dose when combining.
- **Fluvoxamine** inhibits CYP1A2 and raises asenapine levels; smoking induces CYP1A2 but has limited clinical effect on this drug.
- Additive orthostatic hypotension with antihypertensives and additive sedation with opioids, benzodiazepines, and alcohol.
- Modest QT prolongation is additive with Class IA and III antiarrhythmics, methadone, and macrolide antibiotics.
- Contraindicated in severe hepatic impairment and in patients with known hypersensitivity to asenapine or its excipients.

SPECIAL POPULATIONS

- Third-trimester exposure carries the class risk of neonatal extrapyramidal and withdrawal signs; human pregnancy data remain limited.
- Lactation data are sparse, so monitor breastfed infants for sedation and consider better-characterized agents where possible.
- Approved from age 10 for bipolar mania, where the stepwise titration exists specifically to limit sedation and dystonia.
- In older adults expect more orthostasis and sedation, and note that clearance is roughly 30 percent lower than in younger adults.
- No renal adjustment is needed, but Child-Pugh class C hepatic impairment is a contraindication rather than a dose reduction.

PRESCRIBING PEARLS

- Sublingual only: swallowed tablets deliver under 2 percent of the dose and simply do not work.
- No food or drink for 10 minutes after dosing, which is the instruction patients most often forget.
- Consider the Secuado patch when oral numbness rather than efficacy is the reason for failure.

References

Allergan, Inc. (2025). *SAPHRIS (asenapine) sublingual tablets [Prescribing information]*. U.S. Food and Drug Administration. https://dailymed.nlm.nih.gov/dailymed/

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). *Bipolar disorder: Assessment and management* (Clinical guideline CG185). https://www.nice.org.uk/guidance/cg185

National Institute of Diabetes and Digestive and Kidney Diseases. (2023). Asenapine. In *LiverTox: Clinical and research information on drug-induced liver injury*. National Library of Medicine. https://www.ncbi.nlm.nih.gov/books/NBK548092/

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.

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.