TRICYCLIC ANTIDEPRESSANT

Doxepin

Silenor, Sinequan (discontinued), Prudoxin and Zonalon (topical)

Sedating tertiary-amine TCA that is two drugs in one: an antidepressant at 75-300 mg and a selective H1 hypnotic at 3-6 mg.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
Mood 75-150 mg; sleep 3-6 mg	15 h; desmethyl about 31 h	CYP2C19, CYP2D6	Sleep first night; mood 2-4 wks

⚠ FDA BOXED WARNING

Suicidal thoughts and behaviors: antidepressants increased the risk in children, adolescents, and young adults with major depressive disorder and other psychiatric disorders. Monitor closely for clinical worsening and emergence of suicidality, especially early in treatment and after dose changes.

INDICATIONS

- FDA-approved as capsules and oral solution for depression and anxiety, including anxiety or depression associated with alcoholism or organic disease.
- FDA-approved as Silenor 3 mg and 6 mg tablets for insomnia characterized by difficulty with sleep maintenance in adults.
- Approved as topical 5 percent cream for short-term relief of pruritus in atopic dermatitis and lichen simplex chronicus in adults.
- Off-label at low oral doses for chronic urticaria and pruritus, exploiting its extremely potent histamine H1 antagonism.
- Off-label at conventional antidepressant doses for comorbid depression with prominent insomnia, though tolerability limits its use.
- Silenor is the only hypnotic approved for sleep maintenance that is not a scheduled controlled substance in the United States.

DOSING & TITRATION

- For depression start **25-75 mg PO at bedtime** and titrate to a usual range of **75-150 mg/day**, with **300 mg/day** the maximum.
- For insomnia give Silenor **6 mg once daily** within 30 minutes of bedtime, or **3 mg** in adults 65 and older.
- Do not take Silenor within 3 hours of a meal, because food markedly delays absorption and blunts the hypnotic effect.
- Capsules come in 10, 25, 50, 75, 100, and 150 mg strengths; oral concentrate is 10 mg per mL and must be diluted before use.
- Limit Silenor to **3 mg** in patients on strong CYP2D6 inhibitors or with known poor metabolizer status, and in hepatic impairment.
- Taper antidepressant doses gradually when stopping; hypnotic doses of 3 to 6 mg can generally be stopped without a formal taper.

MECHANISM OF ACTION

- One of the most potent histamine H1 antagonists in clinical medicine, which is why single-digit milligram doses produce hypnotic effect.
- At 3 to 6 mg the H1 blockade is essentially selective, avoiding the muscarinic and adrenergic actions that appear at antidepressant doses.
- At 75 mg and above it inhibits both serotonin and norepinephrine reuptake, with the desmethyl metabolite favoring norepinephrine.
- Antidepressant doses add substantial muscarinic and alpha-1 blockade, generating anticholinergic effects, orthostasis, and weight gain.
- Selective H1 antagonism consolidates sleep in the second half of the night without the reinforcing properties of benzodiazepine receptor agonists.

PHARMACOKINETICS

- Rapidly absorbed with peak concentrations at about 3.5 hours for Silenor; a high-fat meal delays the peak and raises exposure substantially.
- Parent half-life is roughly 15 hours and the active metabolite N-desmethyldoxepin averages about 31 hours, so morning grogginess can occur.
- Metabolized principally by CYP2C19 and CYP2D6, with minor contributions from CYP1A2 and CYP2C9 to the overall clearance.
- CYP2D6 poor metabolizers and CYP2C19 poor metabolizers accumulate drug; the Silenor label caps such patients at **3 mg** at bedtime.
- Highly protein bound with extensive tissue distribution, so hemodialysis is not useful and overdose management is entirely supportive.

ADVERSE EFFECTS

- At antidepressant doses sedation, dry mouth, constipation, blurred vision, and weight gain are common and frequently dose limiting.
- At 3 to 6 mg the profile resembles placebo, with somnolence, nausea, and upper respiratory infection the only frequent complaints.
- Orthostatic hypotension at higher doses is a significant fall risk in older adults with cardiovascular disease or polypharmacy.
- Complex sleep behaviors including sleepwalking and sleep driving are described with hypnotics and warrant discontinuation if they occur.
- Antidepressant doses slow cardiac conduction and are dangerous in overdose, producing wide-complex arrhythmia, seizures, and coma.
- Rare reports include agranulocytosis, cholestatic jaundice, and syndrome of inappropriate antidiuretic hormone secretion.

MONITORING

- Obtain a baseline ECG before antidepressant dosing in patients over 50 years or with any known cardiac conduction disease.
- Reassess insomnia after 7 to 10 days on Silenor; failure to improve should prompt evaluation for an underlying medical or psychiatric cause.
- Screen for untreated narrow-angle glaucoma and severe urinary retention before starting either formulation, since both are contraindications.
- Track weight, blood pressure with orthostatics, and anticholinergic symptoms at each visit when using antidepressant doses.
- Monitor for emergent suicidality and mood switch in the first weeks of antidepressant treatment and after each dose increase.

INTERACTIONS & CAUTIONS

- Contraindicated with monoamine oxidase inhibitors and within 14 days of stopping one because of hypertensive crisis and serotonin syndrome.
- Strong CYP2D6 and CYP2C19 inhibitors such as fluoxetine, paroxetine, cimetidine, and fluvoxamine raise concentrations and require dose reduction.
- Additive sedation with alcohol, opioids, benzodiazepines, and Z-drugs; the Silenor label warns against alcohol use entirely.
- Anticholinergic load compounds with antihistamines, oxybutynin, and low-potency antipsychotics, raising delirium risk in older adults.
- At antidepressant doses it adds to QT prolongation from methadone, ondansetron, and class IA or III antiarrhythmic agents.

SPECIAL POPULATIONS

- Pregnancy data are limited; a case report describes neonatal sedation and respiratory depression from breast milk exposure to doxepin.
- Breastfeeding is generally discouraged with doxepin because the long-lived desmethyl metabolite accumulates in nursing infants.
- Silenor is not approved under age 18, and antidepressant doxepin is not established as safe or effective in pediatric patients.
- Use **3 mg** of Silenor in adults 65 and older; Beers Criteria flag doxepin above 6 mg daily as potentially inappropriate in this group.
- Reduce doses in hepatic impairment; no formal renal adjustment exists but metabolites accumulate in advanced kidney disease.

PRESCRIBING PEARLS

- Silenor **3-6 mg** is a selective H1 hypnotic with none of the anticholinergic load of full doses.
- Do not give Silenor within 3 hours of a meal or the hypnotic effect is delayed and blunted.
- The only non-scheduled hypnotic approved specifically for sleep maintenance insomnia.

Verify against the current FDA label and your formulary before prescribing. Educational reference only.

References

American Psychiatric Association. (2010). *Practice guideline for the treatment of patients with major depressive disorder* (3rd ed.). American Psychiatric Publishing. https://psychiatryonline.org/guidelines

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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.