Anafranil

(clomipramine hydrochloride)

Anafranil (clomipramine hydrochloride); not controlled

Full Prescribing Information	DailyMed Drug Information

Summary

Anafranil is a tricyclic antidepressant, clomipramine, supplied only as an oral capsule and approved for obsessive-compulsive disorder from age 10. Benefit builds over weeks, and the label approves no other pediatric use. Cardiac conduction effects, dose-related seizures and lethality in overdose place it behind the SSRIs, which match it for efficacy. Not controlled; brand and generic.

Forms & Strengths

- **Capsules:** 25 mg, 50 mg, 75 mg

Dosing

- **Age:**
  - OCD: 10-17 y/o; not established below age 10.
  - OCD: ≥ 18 y/o, at a higher ceiling.
- **Onset:** 2 to 3 weeks for early effect; judge response after several weeks at a therapeutic dose
- **Duration:** continuous with once-daily dosing
- **Initial Dose:** 25 mg daily, divided, with meals
- **Titration:**
  - First 2 weeks: to 3 mg/kg or 100 mg daily, whichever is smaller.
  - Thereafter: toward the ceiling, allowing 2 to 3 weeks between adjustments.
- **Max Dose:**
  - 10-17 y/o: 3 mg/kg or 200 mg daily, whichever is smaller.

    - ≥ 18 y/o: 250 mg daily.
    - These ceilings limit seizure risk; do not exceed them to chase response.
- **Considerations:** Divide doses with meals during titration, then give the total at bedtime to limit sedation. The mg/kg cap is a seizure limit and moves with weight.

Pharmacology

- **Mechanism:** Tricyclic; inhibits serotonin and, via its active metabolite, norepinephrine reuptake, with muscarinic, histamine H1 and alpha-1 blockade causing most adverse effects
- **Metabolism:** Hepatic, to desmethylclomipramine; half-life 32 hours parent, 69 hours metabolite, so steady state takes 2 to 3 weeks
- **Nonlinear kinetics, a safety property:** exposure is not dose-proportional; above 150 mg/day accumulation can be dramatic, raising dose-dependent seizure risk.
- **Pharmacogenomics:** CYP2D6 poor metabolizers, 7% to 10% of Caucasians, reach 8-fold higher AUC; adding an inhibitor makes a stable patient toxic.
- **Class Positioning:** the only tricyclic with an FDA pediatric indication. Against Zoloft, Prozac and Luvox it adds no efficacy and costs receptor blockade.

Indications

- **Obsessive-Compulsive Disorder** (ICD-10: F42.2, F42.3, F42.8, F42.9): patients 10-17 y/o and adults, where symptoms cause marked distress or impair function

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Off-Label Uses

- **Before anything off-label:** in pediatric OCD an SSRI is as effective and better tolerated. Use Zoloft, Prozac or Luvox with exposure and response prevention first. (AHRQ 2024)
- **Depression in youth** (ICD-10: F32.x, F33.x): not supported; no pre-pubertal benefit, marginal in adolescents. (Cochrane 2013)
- **Looked for, evidence not found:**
    - **Trichotillomania and body-focused repetitive behaviors** (ICD-10: F63.3): adult data only; insufficient in youth.
    - **Repetitive behaviors in autism** (ICD-10: F84.0): insufficient; no graded conclusion.
    - **Cataplexy in narcolepsy** (ICD-10: G47.411): adult tricyclic use; insufficient pediatric evidence.

Contraindications & Warnings

- **Boxed Warning, suicidal thoughts and behaviors:** antidepressants increase suicidal thinking and behavior in children, adolescents and young adults. Monitor closely for clinical worsening; families observe daily.
- **Overdose lethality makes quantity dispensed a prescribing decision.** A tricyclic overdose kills where an SSRI overdose generally does not: the lowest reported fatal dose is 750 mg.
- **Quantity, in practice:** the label twice instructs prescribing the smallest quantity consistent with good patient management. Confirm locked storage at every refill.
- **Dose-related seizure risk, the label's principal risk:** cumulative incidence up to 300 mg/day was 0.64% at 90 days, 1.12% at 180 days, 1.45% at 365 days.
- **Seizure ceilings:** dose predicts risk, hence 250 mg daily maximum in adults, 3 mg/kg or 200 mg daily in youth.
- **Contraindicated:**
  - Hypersensitivity to clomipramine or other tricyclics.
  - An MAOI, linezolid or intravenous methylene blue, or within 14 days of either.
  - The acute recovery period after a myocardial infarction.
- **Use with caution:**
  - Cardiovascular disease, seizure history, brain injury, or a seizure-threshold-lowering drug.
  - Unrecognized bipolar disorder or schizophrenia; mania or psychosis may follow.
  - Hyperthyroidism, liver or renal disease, or adrenal medulla tumors.
  - Planned electroconvulsive therapy or surgery; stop well before, tell the anesthetist.
- **Screen before starting:**
  - Cardiac and family history of sudden death, and a baseline ECG.
  - Seizure history, head injury, and family history of bipolar disorder or suicide.
  - Baseline weight, height, heart rate, and blood pressure sitting and standing.
  - CYP2D6 inhibitors, and who stores the medication at home.

Drug Interactions

- **MAOIs** (phenelzine, tranylcypromine, linezolid, methylene blue): contraindicated. Allow 14 days in either direction.
- **SSRIs** (fluoxetine, sertraline, paroxetine, fluvoxamine): inhibit CYP2D6 and raise clomipramine levels. Use lower doses; allow 5 weeks after stopping fluoxetine.
- **Other CYP2D6 inhibitors** (quinidine, cimetidine, phenothiazines, propafenone, flecainide): a stable patient can turn abruptly toxic. Lower the dose.
- **Other serotonergic drugs** (triptans, fentanyl, lithium, tramadol, buspirone, St John's Wort): serotonin syndrome. Stop both if it occurs.
- **Methylphenidate and other stimulants:** raise tricyclic levels, a live combination in ADHD practice. Titrate slowly, watch cardiac effects.

- **Level shifters** (phenytoin, carbamazepine, haloperidol, warfarin, digoxin, clonidine, alcohol): recheck response, INR or blood pressure after any change.

Administration

- Give in divided doses with meals during titration, for gastrointestinal tolerance.
- After titration, give the total dose at bedtime; 46% of pediatric trial patients reported somnolence.
- Swallow capsules whole; no liquid form exists and they are not opened or divided.
- Allow 2 to 3 weeks between dose adjustments; steady state is not reached sooner.
- Do not stop abruptly; see Discontinuation & Taper.
- Store locked; dispense the smallest quantity consistent with good management, per the label.

Side Effects

- **Common, pediatric trial rates:** dry mouth 63% (placebo 16%), somnolence 46% (11%), dizziness 41% (14%), fatigue 35% (9%), tremor 33% (2%), constipation 22%, anorexia 22%, urinary retention 7%
- **Serious:**
  - Suicidal thinking and behavior, per the boxed warning. Ask directly at every dose change.
  - Seizure, dose related and the label's most significant identified risk. Stop the drug.
  - Cardiac conduction abnormality: 1.5% on treatment against 0.7% on placebo, chiefly ventricular ectopy and conduction delay.
  - Serotonin syndrome, particularly with an MAOI. Stop both drugs.
  - Angle-closure glaucoma, hepatic injury, agranulocytosis.
  - Hyponatremia from SIADH, with reported seizure, coma and death.
  - DRESS, drug rash with eosinophilia and systemic symptoms. Stop immediately.
  - Psychosis, hallucinations, paranoia, precipitated hypomania or mania.
  - Sexual dysfunction, above placebo in males, a common reason adolescents quietly stop.

Monitoring & Labs

- **ECG:** at baseline for unsuspected long QT, at steady state on the target dose, and after every subsequent increase. (AACAP 2012; AHA 1999)
- **ECG thresholds that stop escalation:** heart rate above 130 bpm, PR above 200 ms, QRS above 120 ms, QTc above 460 ms. Hold and refer. (AHA 1999)

- **Suicidality:** every visit for 12 weeks, every dose change, then at least every 3 months. Ask about agitation, hostility and akathisia.
- **Weight, height, blood pressure and heart rate:** baseline, each dose change, every 3 months. Weight sets the 3 mg/kg ceiling.
- **Seizure surveillance:** ask about seizure, aura, staring spell or fall at every visit; reconfirm each new dose stays under the cap.
- **Quantity dispensed and storage:** at every refill, confirm how much is in the home, that it is locked, and who holds it.
- **On trigger:** CY-BOCS every 4 to 6 weeks in titration; sodium for confusion; liver enzymes for jaundice; CBC for fever with sore throat.

Discontinuation & Taper

- **Do not stop abruptly.** The label calls for gradual tapering with careful monitoring.
- Withdrawal brings dizziness, nausea, vomiting, headache, malaise, sleep disturbance, hyperthermia, irritability, psychiatric worsening.
- Long half-lives mean withdrawal may appear days after a reduction; judge each step over a week.
- Discontinue immediately for a seizure, DRESS, symptomatic hyponatremia, or serotonin syndrome.
- Drug holidays are not appropriate; interruption risks withdrawal and relapse.
- OCD is chronic; continue a responder on the lowest effective dose. Benefit held a year under double-blind conditions.

Pregnancy & Lactation

- **Pregnancy:** No adequate controlled studies. Use only if benefit justifies risk, weighing untreated severe OCD. No exposure registry is named.
- **Pregnancy, neonatal:** jitteriness, tremor and seizures reported in neonates exposed until delivery.
- **Lactation:** acceptable on limited evidence; a fully breastfed infant receives about 1.3% to 2.2% of the maternal weight-adjusted dose. (LactMed 2022)
- **Lactation, caveats:** after pregnancy exposure the milk amount may not prevent neonatal withdrawal; better-studied agents exist for depression.

Counseling Points

- **Counsel the family on:**

    - Storing capsules locked, and why the prescription is deliberately small: a tricyclic overdose is dangerous as other medicines are not.
    - Dry mouth, in nearly two thirds of children. Offer sugar-free gum, water and a dental check.
    - Daytime sleepiness early; moving the dose to bedtime is the planned fix.
    - A realistic timeline: little change in the first fortnight; 2 to 3 weeks between changes.
    - Reporting any staring spell, fall or convulsion, since seizure is the dose-limiting risk.
    - Never stopping suddenly, and telling you before planned surgery.
- **Advise them to call for:**
    - New or worsening thoughts of self-harm, or new agitation or hostility.
    - Any seizure, staring spell, or unexplained fall.
    - Fainting, near-fainting, or a racing heartbeat.
    - Fever with sore throat, or rash with fever or facial swelling.
    - Inability to pass urine, or eye pain with blurred vision or halos.

References

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