

CLOZAPINE (Clozaril, FazaClo, Versacloz) Fact Sheet [G]

Bottom Line:

Clozapine is the only drug with convincing evidence of superior efficacy over other antipsychotics for treatment-resistant schizophrenia. Consider using it after two failed trials of other antipsychotics. Side effects can be a real challenge, including severe weight gain, constipation, drooling, sedation, and potential neutropenia.

FDA Indications:

Treatment-resistant schizophrenia; reduction in risk of suicide in schizophrenia and schizoaffective disorder.

Off-Label Uses:

Treatment-resistant bipolar disorder; treatment-resistant aggression and violence.

Dosage Forms:

- **Tablets (Clozaril):** 25 mg (scored), 100 mg (scored).
- **Tablets (G):** 25 mg (scored), 50 mg (scored), 100 mg (scored), 200 mg (scored).
- **Orally disintegrating tablets (FazaClo, [G]):** 12.5 mg, 25 mg, 100 mg, 150 mg, 200 mg.
- **Oral suspension (Versacloz):** 50 mg/mL.

Dosage Guidance:

- Start 12.5 mg once or twice daily; ↑ gradually, in increments of 25–50 mg/day to target dose 300–450 mg/day by end of two weeks; may ↑ further in increments ≤100 mg and no more frequently than once or twice weekly. May require doses as high as 600–900 mg/day; max 900 mg/day (usually in two or three divided doses). May take four to six weeks, or as long as three to six months, for response.
- If dosing is interrupted for ≥48 hours, must be re-titrated from 12.5–25 mg/day; may be increased more rapidly than initial titration, as tolerated.
- Dose timing: Although it can be sedating, many patients develop tolerance and can take it twice daily without significant daytime fatigue.

Monitoring:

- Fasting glucose, lipids.
- Before starting clozapine, ensure absolute neutrophil count (ANC) >1500; for benign ethnic neutropenia population, ensure two baseline ANCs ≥1000. Repeat ANC weekly for first six months, then every two weeks from months six to 12, then monthly after 12 months. If ANC falls below 1500, guidelines become complex depending on how low the value is; consult clozapine Risk Evaluation and Mitigation Strategy (REMS) (www.newclozapinerems.com) for advice.
- Serum level monitoring can be useful; therapeutic response generally occurs at 350–450 ng/mL, though some patients may show response at lower levels. Upper limit is not well defined; increased risk of toxic effects at levels above 750 ng/mL.

Cost: \$\$; oral suspension, ODT: \$\$\$\$

Side Effects (see Table 11 for more detailed information):

- Most common: Sedation, orthostatic hypotension, hypersalivation (place towel on pillow), weight gain (15–30 pound average weight gain after one year), constipation (risk of toxic megacolon if untreated), tachycardia (can treat with propranolol).
- Serious but rare: Potentially life-threatening neutropenia (1%–2%); periodic ANC testing must occur (as above; see prescribing information for monitoring details).
- Pregnancy/breastfeeding: Limited data suggest relative safety in pregnancy; avoid or use caution in breastfeeding.

Mechanism, Pharmacokinetics, and Drug Interactions:

- Dopamine D2 and serotonin 5-HT2A receptor antagonist.
- Metabolized primarily by CYP1A2, also CYP2D6 and CYP3A4; t_{1/2}: 12 hours.
- Avoid use with drugs that may cause bone marrow suppression (eg, carbamazepine, antineoplastics), lower seizure threshold, or have additive anticholinergic effects. Collapse, respiratory arrest, and cardiac arrest reported during initial clozapine treatment in patients taking benzodiazepines. Caution with CYP450 inhibitors and inducers. Smoking increases clozapine clearance by 30%–50%.

Clinical Pearls:

- Risk of neutropenia greatest within first six months, then incidence declines but can still occur.
- Divided doses may minimize some adverse effects (eg, hypotension, seizures).
- A growing number of case reports have been published linking very high clozapine levels to infection. Monitor levels and symptoms of toxicity closely, especially in patients hospitalized for infection.
- FDA-mandated REMS program requires prescribers to be certified to prescribe clozapine (see www.newclozapinerems.com for details).

Fun Fact:

The Quiet Room is a compelling memoir written by patient Lori Schiller, who was an early user of clozapine.