MOOD STABILIZER

Lamotrigine

Lamictal, Lamictal XR, Lamictal ODT, Subvenite

First-line maintenance agent for the depressive pole of bipolar I disorder, weight neutral but bound to a mandatory slow titration.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	TIME TO TARGET
100-200 mg/day PO (bipolar)	25-33 h; 59 h w/ valproate	UGT1A4 glucuronidation	6 weeks minimum titration

⚠ FDA BOXED WARNING

Serious and potentially fatal skin rashes including Stevens-Johnson syndrome and toxic epidermal necrolysis, occurring mostly within the first 8 weeks; risk rises with valproate co-therapy, an excessive starting dose, or faster than recommended escalation. Discontinue at the first sign of rash.

INDICATIONS

- FDA-approved for maintenance treatment of bipolar I disorder in adults to delay the time to recurrence of mood episodes.
- FDA-approved as adjunctive therapy for partial-onset seizures, generalized tonic-clonic seizures, and Lennox-Gastaut syndrome from age 2.
- FDA-approved for conversion to monotherapy in patients aged 16 and older with partial-onset seizures taking a single enzyme-inducing anticonvulsant.
- Off-label acute treatment of bipolar depression, where meta-analysis shows a small but real benefit that grows in more severe depression.
- Off-label augmentation in treatment-resistant unipolar depression and for affective instability in borderline personality disorder.
- It has no antimanic efficacy, so patients with prominent manic recurrence need a different or additional agent.

DOSING & TITRATION

- Standard monotherapy titration is **25 mg/day** for weeks 1-2, **50 mg/day** for weeks 3-4, 100 mg at week 5, and **200 mg/day** at week 6.
- With valproate, halve everything: **25 mg every other day** for weeks 1-2, 25 mg/day weeks 3-4, **50 mg** week 5, then **100 mg/day** target.
- With an enzyme inducer and no valproate, double it: **50 mg/day** weeks 1-2, **100 mg/day** weeks 3-4, then increase to a target of **400 mg/day**.
- Never exceed these steps; escalating faster or starting higher is the single most avoidable cause of serious rash.
- If therapy lapses for more than 5 half-lives, roughly 5 days, restart the entire titration from the beginning rather than resuming the prior dose.
- Reduce the maintenance dose in significant renal impairment and by 25 to 75 percent in moderate to severe hepatic impairment.

MECHANISM OF ACTION

- Blocks voltage-gated sodium channels in the inactivated state, stabilizing neuronal membranes and reducing repetitive high-frequency firing.
- Inhibits presynaptic glutamate and aspartate release, an effect proposed to underlie the antidepressant and antikindling actions.
- Modulates high-voltage-activated calcium channels, further reducing excitatory transmission without direct GABA receptor effects.
- Absence of significant histamine, muscarinic, or adrenergic blockade explains the weight neutrality and minimal sedation.
- The gradual onset over weeks reflects both the mandated slow titration and downstream changes in glutamatergic signaling.

PHARMACOKINETICS

- Oral bioavailability is essentially complete and unaffected by food, with peak plasma concentrations at 1 to 5 hours.
- Metabolism is by UGT1A4 glucuronidation with renal excretion of the conjugate; there are no clinically important CYP interactions.
- The half-life is 25 to 33 hours on monotherapy, roughly 59 hours when valproate inhibits glucuronidation, and about 13 hours with inducers.
- Estrogen-containing contraceptives induce glucuronidation and cut lamotrigine levels by about half, with rebound during the pill-free week.
- Clearance rises up to two- to threefold during pregnancy and returns to baseline within weeks postpartum, requiring planned dose changes.

ADVERSE EFFECTS

- Benign maculopapular rash occurs in about 10 percent, typically in weeks 2 to 8, and cannot be reliably distinguished early from serious rash.
- Serious rash requiring hospitalization occurs in roughly 0.08 to 0.3 percent of adults and 0.3 to 0.8 percent of children aged 2 to 16.
- Headache, dizziness, nausea, diplopia, ataxia, and insomnia are common and generally dose-related during titration.
- It is weight neutral and largely free of sexual dysfunction, which is a major reason for its acceptability in maintenance therapy.
- Rare serious events include aseptic meningitis, hemophagocytic lymphohistiocytosis, blood dyscrasias, and multiorgan hypersensitivity.
- In vitro class IB sodium channel blockade underlies an arrhythmia warning for patients with structural or ischemic heart disease.

MONITORING

- Counsel at every titration visit to stop the drug and call immediately for any rash, especially with fever, mucosal lesions, or facial swelling.
- No routine serum levels or laboratory monitoring is required for mood indications in otherwise healthy adults.
- Check levels when clearance changes are expected, notably during pregnancy, postpartum, or when a contraceptive is started or stopped.
- Consider an ECG before starting in patients with known structural heart disease, conduction disease, or clinically significant ischemia.
- Monitor for persistent fever, rash, hepatosplenomegaly, and cytopenias, which suggest hemophagocytic lymphohistiocytosis and require urgent workup.

INTERACTIONS & CAUTIONS

- Valproate inhibits glucuronidation and roughly doubles lamotrigine levels, so the starting dose and target must be halved.
- Carbamazepine, phenytoin, phenobarbital, primidone, and rifampin induce glucuronidation and roughly halve lamotrigine concentrations.
- Combined oral contraceptives lower levels by about 50 percent; stopping the pill without lowering the lamotrigine dose can cause toxicity.
- Lamotrigine modestly raises carbamazepine epoxide concentrations in some patients, producing diplopia and dizziness at unchanged doses.
- Avoid rapid dose escalation with any interacting drug, and treat every dose change in an interacting agent as a reason to reassess.

SPECIAL POPULATIONS

- Lamotrigine has among the most reassuring pregnancy registry data of the anticonvulsants, without a clear malformation signal at usual doses.
- Clearance can triple by the third trimester, so check levels each trimester and plan a rapid postpartum taper toward the preconception dose.
- Relative infant dose in breast milk is comparatively high; monitor the nursing infant for rash, sedation, and poor feeding.
- Pediatric patients aged 2 to 16 have several times the adult risk of serious rash, so titration discipline matters even more.
- Older adults tolerate lamotrigine well overall, but reduce doses when renal or hepatic function is impaired.

PRESCRIBING PEARLS

- Miss 5 days of doses and you must restart the full titration; do not resume at the old dose.
- Adding valproate halves the lamotrigine dose; adding carbamazepine roughly doubles it.
- Any rash in the first 8 weeks means stop the drug now and evaluate, not watch and wait.

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.