LAMOTRIGINE

**Brands**  
- Lamictal  
- Labileno  
- Lamictin  
*see index for additional brand names*

**Class**  
- Neuroscience-based Nomenclature: glutamate, voltage-gated sodium channel blocker (Glu-CB)  
- Anticonvulsant, mood stabilizer, voltage-sensitive sodium channel antagonist

**Commonly Prescribed for**  
(italic for FDA approved)  
- Maintenance treatment of bipolar I disorder  
- Partial seizures (adjunctive; adults and children ages 2 and older)  
- Generalized seizures of Lennox-Gastaut syndrome (adjunctive; adults and children ages 2 and older)  
- Primary generalized tonic-clonic seizures (adjunctive; adults and children ages 2 and older)  
- Conversion to monotherapy in adults (16 and older) with partial seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate  
- Bipolar depression  
- Bipolar mania (adjunctive and second-line)  
- Psychosis, schizophrenia (adjunctive)  
- Neuropathic pain/chronic pain  
- Major depressive disorder (adjunctive)  
- Other seizure types and as initial monotherapy for epilepsy

**How the Drug Works**  
- Acts as a use-dependent blocker of voltage-sensitive sodium channels  
- Interacts with the open channel conformation of voltage-sensitive sodium channels  
- Interacts at a specific site of the alpha pore-forming subunit of voltage-sensitive sodium channels  
- Inhibits release of glutamate and asparate

**How Long Until It Works**  
- May take several weeks to improve bipolar depression

**Generic?**  Yes

**If It Works**  
- The goal of treatment is complete remission of symptoms (e.g., seizures, depression, pain)  
- Continue treatment until all symptoms are gone or until improvement is stable and then continue treating indefinitely as long as improvement persists  
- Continue treatment indefinitely to avoid recurrence of mania, depression, and/or seizures  
- Treatment of chronic neuropathic pain may reduce but does not eliminate pain symptoms and is not a cure since pain usually recurs after medicine stopped

**If It Doesn’t Work (for bipolar disorder)**  
- Many patients have only a partial response where some symptoms are improved but others persist or continue to wax and wane without stabilization of mood  
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory  
- Consider increasing dose, switching to another agent, or adding an appropriate augmenting agent  
- Consider adding psychotherapy  
- Consider biofeedback or hypnosis for pain  
- Consider the presence of noncompliance and counsel patient  
- Switch to another mood stabilizer with fewer side effects  
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)

**Best Augmenting Combos for Partial Response or Treatment Resistance (for bipolar disorder)**  
- Lithium  
- Atypical antipsychotics (especially risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole)  
- Valproate (with caution and at half dose of lamotrigine in the presence of valproate,
because valproate can double lamotrigine levels)

**Antidepressants** (with caution because antidepressants can destabilize mood in some patients, including induction of rapid cycling or suicidal ideation; in particular consider bupropion; also SSRIs, SNRIs, others; generally avoid TCAs, MAOIs)

**Tests**
- None required
- The value of monitoring plasma concentrations of lamotrigine has not been established
- Because lamotrigine binds to melanin-containing tissues, ophthalmological checks may be considered

### SIDE EFFECTS

**How Drug Causes Side Effects**
- CNS side effects theoretically due to excessive actions at voltage-sensitive sodium channels
- Rash hypothetically an allergic reaction

**Notable Side Effects**
- Benign rash (approximately 10%)
- Dose dependent: blurred or double vision, dizziness, ataxia
- Sedation, headache, tremor, insomnia, poor coordination, fatigue
- Nausea (dose-dependent), vomiting, dyspepsia, rhinitis
- Additional effects in pediatric patients with epilepsy: infection, pharyngitis, asthenia

**Life-Threatening or Dangerous Side Effects**
- Rare serious rash (risk may be greater in pediatric patients but still rare)
- Rare multi-organ failure associated with Stevens-Johnson syndrome, toxic epidermal necrolysis, or drug hypersensitivity syndrome
- Rare blood dyscrasias
- Rare aseptic meningitis
- Rare sudden unexplained deaths have occurred in epilepsy (unknown if related to lamotrigine use)
- Withdrawal seizures upon abrupt withdrawal
- Rare activation of suicidal ideation and behavior (suicidality)

### Weight Gain
- Reported but not expected

### Sedation
- Reported but not expected
- Dose-related
- Can wear off with time

**What to Do About Side Effects**
- Wait
- Take at night to reduce daytime sedation
- Divide dosing to twice daily
- If patient develops signs of a rash with benign characteristics (i.e., a rash that peaks within days, settles in 10–14 days, is spotty, nonconfluent, nontender, has no systemic features, and laboratory tests are normal):
  - Reduce lamotrigine dose or stop dosage
  - Warn patient to stop drug and contact physician if rash worsens or new symptoms emerge
  - Prescribe antihistamine and/or topical corticosteroid for pruritis
  - Monitor patient closely
- If patient develops signs of a rash with serious characteristics (i.e., a rash that is confluent and widespread, or purpuric or tender; with any prominent involvement of neck or upper trunk; any involvement of eyes, lips, mouth, etc.; any associated fever, malaise, pharyngitis, anorexia, or lymphadenopathy; abnormal laboratory tests for complete blood count, liver function, urea, creatinine):
  - Stop lamotrigine (and valproate if administered)
  - Monitor and investigate organ involvement (hepatic, renal, hematologic)
  - Patient may require hospitalization
  - Monitor patient very closely

### Best Augmenting Agents for Side Effects
- Antihistamines and/or topical corticosteroid for rash, pruritis
- Many side effects cannot be improved with an augmenting agent
**LAMOTRIGINE**

### Usual Dosage Range

- **Monotherapy for bipolar disorder:**
  100–200 mg/day

- **Adjunctive treatment for bipolar disorder:**
  100 mg/day in combination with valproate; 400 mg/day in combination with enzyme-inducing antiepileptic drugs such as carbamazepine, phenobarbital, phenytoin, and primidone

- **Monotherapy for seizures in patients over age 12:**
  300–500 mg/day in 2 doses

- **Adjunctive treatment for seizures in patients over age 12:**
  100–200 mg/day for regimens containing valproate; 100–200 mg/day for valproate alone; 300–500 mg/day in 2 doses for regimens not containing valproate

- **Patients ages 2–12 with epilepsy are dosed based on body weight and concomitant medications**

### Dosage Forms

- **Tablet** 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg

- **Chewable tablet** 2 mg, 5 mg, 25 mg, 100 mg

- **Orally disintegrating tablet** 25 mg, 50 mg, 100 mg, 200 mg

- **Extended-release tablet** 25 mg, 50 mg, 100 mg, 200 mg, 250 mg, 300 mg

### How to Dose

- **Bipolar disorder (monotherapy, see chart):** for the first 2 weeks administer

### Dosing Schedule for Lamotrigine Monotherapy

<table>
<thead>
<tr>
<th>Week</th>
<th>Dose (mg/day)</th>
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<tbody>
<tr>
<td>0</td>
<td>25</td>
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<tr>
<td>1</td>
<td>50</td>
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<tr>
<td>2</td>
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<td>3</td>
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<td>5</td>
<td>200</td>
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<td>6</td>
<td>200</td>
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* 25 mg/day; at week 3 increase to 50 mg/day; at week 5 increase to 100 mg/day; at week 6 increase to 200 mg/day; maximum dose generally 200 mg/day

* Bipolar disorder (adjunct to valproate): for the first 2 weeks administer 25 mg every other day; at week 3 increase to 50 mg/day; at week 5 increase to 100 mg/day; at week 6 increase to 100 mg/day; maximum dose generally 100 mg/day

* Bipolar disorder (adjunct to enzyme-inducing antiepileptic drugs): for the first 2 weeks administer 50 mg/day; at week 3 increase to 100 mg/day in divided doses; starting at week 5 increase by 100 mg/day each week; maximum dose generally 400 mg/day in divided doses

* When lamotrigine is added to epilepsy treatment that includes valproate (ages 12 and older): for the first 2 weeks administer 25 mg every other day; at week 3 increase to 25 mg/day; every 1–2 weeks can increase by 25–50 mg/day; usual maintenance dose 100–400 mg/day in 1–2 doses or 100–200 mg/day if lamotrigine is added to valproate alone

* When lamotrigine is added to epilepsy treatment that includes carbamazepine, phenytoin, phenobarbital, or primidone (without valproate) (ages 12 and older): for the first 2 weeks administer 50 mg/day; at week 3 increase to 100 mg/day in 2 doses; every 1–2 weeks can increase by 100 mg/day; usual maintenance dose 300–500 mg/day in 2 doses
• When converting from a single enzyme-inducing antiepileptic drug to lamotrigine monotherapy for epilepsy: titrate as described above to 500 mg/day in 2 doses while maintaining dose of previous medication; decrease first drug in 20% decrements each week over the next 4 weeks
• When converting from valproate to lamotrigine monotherapy for epilepsy: titrate as described above to 200 mg/day while maintaining dose of valproate, then gradually increase lamotrigine up to 500 mg/day while gradually discontinuing valproate
• Seizures (under age 12): see Children and Adolescents

Dosing Tips

• Very slow dose titration may reduce the incidence of skin rash
• Therefore, dose should not be titrated faster than recommended because of possible risk of increased side effects, including rash
• If patient stops taking lamotrigine for 5 days or more it may be necessary to restart the drug with the initial dose titration, as rashes have been reported on reexposure
• Advise patient to avoid new medications, foods, or products during the first 3 months of lamotrigine treatment in order to decrease the risk of unrelated rash; patient should also not start lamotrigine within 2 weeks of a viral infection, rash, or vaccination
• If lamotrigine is added to patients taking valproate, remember that valproate inhibits lamotrigine metabolism and therefore titration rate and ultimate dose of lamotrigine should be reduced by 50% to reduce the risk of rash
• Thus, if concomitant valproate is discontinued after lamotrigine dose is stabilized, then the lamotrigine dose should be cautiously doubled over at least 2 weeks in equal increments each week following discontinuation of valproate
• Also, if concomitant enzyme-inducing antiepileptic drugs such as carbamazepine, phenobarbital, phenytoin, and primidone are discontinued after lamotrigine dose is stabilized, then the lamotrigine dose should be maintained for 1 week following discontinuation of the other drug and then reduced by half over 2 weeks in equal decrements each week
• Since oral contraceptives and pregnancy can decrease lamotrigine levels, adjustments to the maintenance dose of lamotrigine are recommended in women taking, starting, or stopping oral contraceptives, becoming pregnant, or after delivery
• Chewable dispersible tablets should only be administered as whole tablets; dose should be rounded down to the nearest whole tablet
• Chewable dispersible tablets can be dispersed by adding the tablet to liquid (enough to cover the drug); after approximately 1 minute the solution should be stirred and then consumed immediately in its entirety
• Do not break or chew extended-release tablets, as this could alter controlled-release properties

Overdose

• Some fatalities have occurred; ataxia, nystagmus, seizures, coma, intraventricular conduction delay

Long-Term Use

• Safe

Habit Forming

• No

How to Stop

• Taper over at least 2 weeks
• Rapid discontinuation can increase the risk of relapse in bipolar disorder
• Patients with epilepsy may seize upon withdrawal, especially if withdrawal is abrupt
• Discontinuation symptoms uncommon

Pharmacokinetics

• Elimination half-life in healthy volunteers approximately 33 hours after a single dose of lamotrigine
• Elimination half-life in patients receiving concomitant valproate treatment

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Patient should be instructed to report any symptoms of hypersensitivity immediately (fever; flu-like symptoms; rash; blisters on skin or in eyes, mouth, nose, or genital areas; swelling of eyelids, conjunctivitis, lymphadenopathy)

Aseptic meningitis has been reported rarely in association with lamotrigine use.

Patients should be advised to report any symptoms of aseptic meningitis immediately; these include headache, chills, fever, vomiting and nausea, a stiff neck, and sensitivity to light.

Depressive effects may be increased by other CNS depressants (alcohol, MAOIs, other anticonvulsants, etc.)

A small number of people may experience a worsening of seizures.

May cause photosensitivity.

Lamotrigine binds to tissue that contains melanin, so for long-term treatment ophthalmological checks may be considered.

Warn patients and their caregivers about the possibility of activation of suicidal ideation and advise them to report such side effects immediately.

Do Not Use

If there is a proven allergy to lamotrigine approximately 59 hours after a single dose of lamotrigine

• Elimination half-life in patients receiving concomitant enzyme-inducing antiepileptic drugs (such as carbamazepine, phenobarbital, phenytoin, and primidone) approximately 14 hours after a single dose of lamotrigine

• Metabolized in the liver through glucuronidation but not through the CYP450 enzyme system

• Inactive metabolite

• Renally excreted

• Lamotrigine inhibits dihydrofolate reductase and may therefore reduce folate concentrations

• Rapidly and completely absorbed; bioavailability not affected by food

**Drug Interactions**

• Valproate increases plasma concentrations and half-life of lamotrigine, requiring lower doses of lamotrigine (half or less)

• Use of lamotrigine with valproate may be associated with an increased incidence of rash

• Enzyme-inducing antiepileptic drugs (e.g., carbamazepine, phenobarbital, phenytoin, primidone) may increase the clearance of lamotrigine and lower its plasma levels

• Oral contraceptives may decrease plasma levels of lamotrigine

• No likely pharmacokinetic interactions of lamotrigine with lithium, oxcarbazepine, atypical antipsychotics, or antidepressants

• False-positive urine immunoassay screening tests for phencyclidine (PCP) have been reported in patients taking lamotrigine due to a lack of specificity of the screening tests

**Other Warnings/Precautions**

• Life-threatening rashes have developed in association with lamotrigine use; lamotrigine should generally be discontinued at the first sign of serious rash

• Risk of rash may be increased with higher doses, faster dose escalation, concomitant use of valproate, or in children under age 12

• Patient should be instructed to report any symptoms of hypersensitivity immediately (fever; flu-like symptoms; rash; blisters on skin or in eyes, mouth, ears, nose, or genital areas; swelling of eyelids, conjunctivitis, lymphadenopathy)

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**SPECIAL POPULATIONS**

**Renal Impairment**

• Lamotrigine is renally excreted, so the maintenance dose may need to be lowered

• Can be removed by hemodialysis; patients receiving hemodialysis may require supplemental doses of lamotrigine

**Hepatic Impairment**

• Dose adjustment not necessary in mild impairment

• Initial, escalation, and maintenance doses should be reduced by 25% in patients with moderate and severe liver impairment without ascites and 50% in patients with severe liver impairment with ascites

**Cardiac Impairment**

• Clinical experience is limited

• Drug should be used with caution

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- Clinical experience is limited.
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**Elderly**
- Some patients may tolerate lower doses better
- Elderly patients may be more susceptible to adverse effects

**Children and Adolescents**
- Ages 2 and older: approved as add-on for Lennox-Gastaut syndrome
- Ages 2 and older: approved as add-on for partial seizures
- No other use of lamotrigine is approved for patients under 16 years of age
- Risk of rash is increased in pediatric patients, especially in children under 12 and in children taking valproate
- When lamotrigine is added to treatment that includes valproate (ages 2–12): for the first 2 weeks administer 0.15 mg/kg per day in 1–2 doses rounded down to the nearest whole tablet; at week 3 increase to 0.3 mg/kg per day in 1–2 doses rounded down to the nearest whole tablet; every 1–2 weeks can increase by 0.3 mg/kg per day rounded down to the nearest whole tablet; usual maintenance dose 1–5 mg/kg per day in 1–2 doses (maximum generally 200 mg/day) or 1–3 mg/kg per day in 1–2 doses if lamotrigine is added to valproate alone
- When lamotrigine is added to treatment with carbamazepine, phenytoin, phenobarbital, or primidone (without valproate) (ages 2–12): for the first 2 weeks administer 0.6 mg/kg per day in 2 doses rounded down to the nearest whole tablet; at week 3 increase to 1.2 mg/kg per day in 2 doses rounded down to the nearest whole tablet; every 1–2 weeks can increase by 1.2 mg/kg per day rounded down to the nearest whole tablet; usual maintenance dose 5–15 mg/kg per day in 2 doses (maximum dose generally 400 mg per day)
- Clearance of lamotrigine may be influenced by weight, such that patients weighing less than 30 kg may require an increase of up to 50% for maintenance doses

**Pregnancy**
- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information

**Breast Feeding**
- Some drug is found in mother’s breast milk
- Generally recommended either to discontinue drug or bottle feed
- If drug is continued while breast feeding, infant should be monitored for possible adverse effects

in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001

- Controlled studies have not been conducted in pregnant women
- Use in women of childbearing potential requires weighing potential benefits to the mother against the risks to the fetus
- Pregnancy registry data show increased risk of isolated cleft palate or cleft lip deformity with first trimester exposure
- If treatment with lamotrigine is continued, plasma concentrations of lamotrigine may be reduced during pregnancy, possibly requiring increased doses with dose reduction following delivery
- Pregnancy exposure registry for lamotrigine: (800) 336–2176
- Taper drug if discontinuing
- Seizures, even mild seizures, may cause harm to the embryo/fetus
- Recurrent bipolar illness during pregnancy can be quite disruptive
- For bipolar patients, lamotrigine should generally be discontinued before anticipated pregnancies
- For bipolar patients in whom treatment is discontinued, given the risk of relapse in the postpartum period, lamotrigine should generally be restarted immediately after delivery
- Atypical antipsychotics may be preferable to lithium or anticonvulsants such as lamotrigine if treatment of bipolar disorder is required during pregnancy, but lamotrigine may be preferable to other anticonvulsants such as valproate if anticonvulsant treatment is required during pregnancy
- Bipolar symptoms may recur or worsen during pregnancy and some form of treatment may be necessary

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convincing evidence of efficacy in bipolar disorder (e.g., gabapentin or topiramate) ✴️ Low levels of use may be based upon exaggerated fears of skin rashes or lack of knowledge about how to manage skin rashes if they occur ✴️ May actually be one of the best tolerated mood stabilizers with little weight gain or sedation • Actual risk of serious skin rash may be comparable to agents erroneously considered “safer” including carbamazepine, phenytoin, phenobarbital, and zonisamide • Rashes are common even in placebo-treated patients in clinical trials of bipolar patients (5–10%) due to non-drug related causes including eczema, irritant, and allergic contact dermatitis, such as poison ivy and insect bite reactions ✴️ To manage rashes in bipolar patients receiving lamotrigine, realize that rashes that occur within the first 5 days or after 8–12 weeks of treatment are rarely drug-related, and learn the clinical distinctions between a benign rash and a serious rash (see What to Do About Side Effects section) • Rash, including serious rash, appears riskiest in younger children, in those who are receiving concomitant valproate, and/or in those receiving rapid lamotrigine titration and/or high dosing • Risk of serious rash is less than 1% and has been declining since slower titration, lower dosing, adjustments to use of concomitant valproate administration, and limitations on use in children under 12 have been implemented • Incidence of serious rash is very low (approaching zero) in recent studies of bipolar patients • Benign rashes related to lamotrigine may affect up to 10% of patients and resolve rapidly with drug discontinuation ✴️ Given the limited treatment options for bipolar depression, patients with benign rashes can even be rechallenged with lamotrigine 5–12 mg/day with very slow titration after risk/benefit analysis if they are informed, reliable, closely monitored, and warned to stop lamotrigine and contact their physician if signs of hypersensitivity occur
• Only a third of bipolar patients experience adequate relief with a monotherapy, so most patients need multiple medications for best control
• Lamotrigine is useful in combination with atypical antipsychotics and/or lithium for acute mania
• Usefulness for bipolar disorder in combination with anticonvulsants other than valproate is not well demonstrated; such combinations can be expensive and are possibly ineffective or even irrational

• May be useful as an adjunct to atypical antipsychotics for rapid onset of action in schizophrenia
• May be useful as an adjunct to antidepressants in major depressive disorder
• Early studies suggest possible utility for patients with neuropathic pain such as diabetic peripheral neuropathy, HIV-associated neuropathy, and other pain conditions including migraine

Suggested Reading


