**LAMOTRIGINE:**

Class: Anticonvulsant

**Indications:**

_U.S. labeling:_ Adjunctive therapy in the treatment of generalized seizures of Lennox-Gastaut syndrome, primary generalized tonic-clonic seizures, and partial seizures; conversion to monotherapy in patients with partial seizures who are receiving treatment with a single antiepileptic drug (AED) (specifically carbamazepine, phenytoin, phenobarbital, primidone, or valproic acid); maintenance treatment of bipolar I disorder

Extended release: Adjunctive therapy for primary generalized tonic-clonic seizures and partial seizures (with or without secondary generalization); conversion to monotherapy in patients with partial seizures who are receiving treatment with a single antiepileptic drug AED

_Canadian labeling:_ Immediate release: Adjunctive therapy for epilepsy uncontrolled by conventional therapy; monotherapy of epilepsy following withdrawal of concurrent antiepileptic agents; adjunctive therapy for Lennox-Gastaut syndrome

**Available dosage form in the hospital:** TAB(25MG, 50MG,100MG), 5 MG LIQUITAB

**Trade Names:**

**Dosage:**

- **Lennox-Gastaut (adjunctive):** Oral:

  **Immediate release formulation:**

  - Regimens not containing carbamazepine, phenytoin, phenobarbital, primidone, or valproic acid:
    Initial: Weeks 1 and 2: 25 mg once daily; Weeks 3 and 4: 50 mg once daily; Week 5 and beyond: Increase by 50 mg daily every 1-2 weeks; Usual maintenance: 225-375 mg daily in 2 divided doses
  - Regimens containing valproic acid: Initial: Weeks 1 and 2: 25 mg _every other_ day; Weeks 3 and 4: 25 mg once daily; Week 5 and beyond: Increase by 25-50 mg daily every 1-2 weeks; Usual maintenance: 100-200 mg daily (valproic acid alone) or 100-400 mg daily (valproic acid and other drugs that induce glucuronidation) in 1 or 2 divided doses
  - Regimens containing carbamazepine, phenytoin, phenobarbital, or primidone and without valproic acid: Initial: Weeks 1 and 2: 50 mg once daily; Weeks 3 and 4: 100 mg daily in 2 divided doses; Week 5 and beyond: Increase by 100 mg daily every 1-2 weeks; Usual maintenance: 300-500 mg daily in 2 divided doses; maximum daily dose: 700 mg

- **Partial seizures (adjunctive) and primary generalized tonic-clonic seizures (adjunctive):** Oral:

  **Immediate release formulation:**

  - Regimens not containing carbamazepine, phenytoin, phenobarbital, primidone, or valproic acid:
    Initial: Weeks 1 and 2: 25 mg once daily; Weeks 3 and 4: 50 mg once daily; Week 5 and beyond: Increase by 50 mg daily every 1-2 weeks; Usual maintenance: 225-375 mg daily in 2 divided doses
  - Regimens containing valproic acid: Initial: Weeks 1 and 2: 25 mg _every other_ day; Weeks 3 and 4: 25 mg once daily; Week 5 and beyond: Increase by 25-50 mg daily every 1-2 weeks; Usual maintenance: 100-200 mg daily (valproic acid alone) or 100-400 mg daily (valproic acid and other drugs that induce glucuronidation) in 1 or 2 divided doses
  - Regimens containing carbamazepine, phenytoin, phenobarbital, or primidone and without valproic acid: Initial: Weeks 1 and 2: 50 mg once daily; Weeks 3 and 4: 100 mg daily in 2 divided doses; Week 5 and beyond: Increase by 100 mg daily every 1-2 weeks; Usual maintenance: 300-500 mg daily in 2 divided doses; maximum daily dose: 700 mg
**Extended release formulation:**

- **Regimens not containing** carbamazepine, phenytoin, phenobarbital, primidone, or valproic acid:
  Initial: Weeks 1 and 2: 25 mg once daily; Weeks 3 and 4: 50 mg once daily; Week 5: 100 mg once daily; Week 6: 150 mg once daily; Week 7: 200 mg once daily; Week 8 and beyond: Dose increases should not exceed 100 mg daily at weekly intervals; Usual maintenance: 300-400 mg once daily
- **Regimens containing** valproic acid:
  Initial: Weeks 1 and 2: 25 mg every other day; Weeks 3 and 4: 25 mg once daily; Week 5: 50 mg once daily; Week 6: 100 mg once daily; Week 7: 150 mg once daily; Week 8 and beyond: Dose increases should not exceed 100 mg daily at weekly intervals; Usual maintenance: 200-250 mg once daily
- **Regimens containing** carbamazepine, phenytoin, phenobarbital, or primidone and without valproic acid:
  Initial: Weeks 1 and 2: 50 mg once daily; Weeks 3 and 4: 100 mg once daily; Week 5: 200 mg once daily; Week 6: 300 mg once daily; Week 7: 400 mg once daily; Week 8 and beyond: Dose increases should not exceed 100 mg daily at weekly intervals; Usual maintenance: 400-600 mg once daily

**Conversion strategy from adjunctive therapy with valproic acid to monotherapy with lamotrigine:**

**Immediate release formulation:**
- Initiate and titrate as per escalation recommendations for adjunctive therapy to a lamotrigine dose of 200 mg daily.
- Then taper valproic acid dose in decrements of not >500 mg/day/week to a valproic acid dosage of 500 mg daily; this dosage should be maintained for 1 week. The lamotrigine dosage should then be increased to 300 mg daily while valproic acid is simultaneously decreased to 250 mg daily; this dosage should be maintained for 1 week.
- Valproic acid may then be discontinued, while the lamotrigine dose is increased by 100 mg daily at weekly intervals to achieve a lamotrigine maintenance dose of 500 mg daily in 2 divided doses.

**Extended release formulation:**
- Initiate and titrate as per escalation recommendations for adjunctive therapy to a lamotrigine dose of 150 mg daily.
- Then taper valproic acid dose in decrements of not >500 mg/day/week to a valproic acid dosage of 500 mg daily; this dosage should be maintained for 1 week. The lamotrigine dosage should then be increased to 200 mg daily while valproic acid is simultaneously decreased to 250 mg daily; this dosage should be maintained for 1 week.
- Valproic acid may then be discontinued, while the lamotrigine dose is increased to achieve a maintenance dosage range of 250-300 mg once daily.

**Conversion strategy from adjunctive therapy with carbamazepine, phenytoin, phenobarbital, or primidone to monotherapy with lamotrigine:**

**Immediate release formulation and extended release formulation:**
- Initiate and titrate as per escalation recommendations for adjunctive therapy to a lamotrigine dose of 500 mg daily.
- Concomitant enzyme-inducing AED should then be withdrawn by 20% decrements each week over a 4-week period.
- Following withdrawal of the enzyme-inducing AED (eg, ~2 weeks later for extended release; 1 week later for immediate release), the dosage of lamotrigine may be tapered in decrements of not >100 mg daily at 1-week intervals to achieve a maintenance dosage range of 250-300 mg once daily (extended release) or 200 mg daily (immediate release) as clinically indicated.
Conversion strategy from adjunctive therapy with AED other than carbamazepine, phenytoin, phenobarbital, primidone or valproic acid to monotherapy with lamotrigine:

**Immediate release formulation:** No specific guidelines available

**Extended release formulation:** Initiate and titrate as per escalation recommendations for adjunctive therapy to a lamotrigine dose of 250-300 mg daily. Concomitant AED should then be withdrawn by 20% decrements each week over a 4-week period.

Conversion from immediate release to extended release (Lamictal® XR™): Initial dose of the extended release tablet should match the total daily dose of the immediate-release formulation. Adjust dose as needed within the recommended dosing guidelines.

-Bipolar disorder: Oral:

**Immediate release formulation:**
- Regimens not containing carbamazepine, phenytoin, phenobarbital, primidone, or valproic acid:
  - Initial: Weeks 1 and 2: 25 mg once daily; Weeks 3 and 4: 50 mg once daily; Week 5: 100 mg once daily; Week 6 and maintenance: 200 mg once daily
- Regimens containing valproic acid:
  - Initial: Weeks 1 and 2: 25 mg every other day; Weeks 3 and 4: 25 mg once daily; Week 5: 50 mg once daily; Week 6 and maintenance: 100 mg once daily
- Regimens containing carbamazepine, phenytoin, phenobarbital, or primidone and without valproic acid:
  - Initial: Weeks 1 and 2: 50 mg once daily; Weeks 3 and 4: 100 mg daily in divided doses; Week 5: 200 mg daily in divided doses; Week 6: 300 mg daily in divided doses
  - Maintenance: up to 400 mg daily in divided doses

*Adjustment following discontinuation of psychotropic medication:
- Discontinuing valproic acid with current dose of lamotrigine 100 mg daily: 150 mg daily for week 1, then increase to 200 mg daily beginning week 2
- Discontinuing carbamazepine, phenytoin, phenobarbital, primidone, or rifampin with current dose of lamotrigine 400 mg daily: 400 mg daily for week 1, then decrease to 300 mg daily for week 2, then decrease to 200 mg daily beginning week 3

Canadian labeling:
- Uncontrolled epilepsy (adjunctive) or Lennox-Gastaut syndrome (adjunctive): Oral: Note: AED that induce lamotrigine glucuronidation include carbamazepine, phenytoin, phenobarbital, and primidone. Antiepileptic agents that do not induce or inhibit lamotrigine glucuronidation include oxcarbazepine, felbamate, levetiracetam, gabapentin, topiramate, zonisamide, pregabalin. Valproic acid inhibits lamotrigine glucuronidation.
- Regimens containing inducers of lamotrigine glucuronidation and valproic acid or regimens not containing agents that induce or inhibit lamotrigine glucuronidation:
  - Initial: Weeks 1 and 2: 25 mg once daily; Weeks 3 and 4: 25 mg twice daily; Week 5 and beyond: Increase dose by 25-50 mg every 1-2 weeks until maintenance dose established (usual maintenance dose: 100-200 mg daily in 2 divided doses)
- Regimens containing inducers of lamotrigine glucuronidation and without valproic acid:
  - Initial: Weeks 1 and 2: 50 mg once daily; Weeks 3 and 4: 50 mg twice daily; Week 5 and beyond: Increase dose by 100 mg every 1-2 weeks until maintenance dose established (usual maintenance dose: 300-500 mg daily in 2 divided doses)
- Conversion from adjunctive therapy with concomitant AEDs for epilepsy to lamotrigine monotherapy: Decrease dose of concomitant antiepileptic agent by ~20% of original dose every week for 5 weeks (slower taper may be considered if clinically indicated). Lamotrigine dosage adjustments during this period should be determined by changes in lamotrigine pharmacokinetics due to withdrawal of the concomitant AED, and by the clinical response of patient.

Additional considerations:
- Discontinuing therapy: Decrease dose by ~50% per week, over at least 2 weeks unless safety concerns require a more rapid withdrawal. Discontinuing carbamazepine, phenytoin, phenobarbital, primidone,
or rifampin should prolong the half-life of lamotrigine; discontinuing valproic acid should shorten the half-life of lamotrigine

**Restarting therapy after discontinuation:** If lamotrigine has been withheld for >5 half-lives, consider restarting according to initial dosing recommendations. **Note:** Concomitant medications may affect the half-life of lamotrigine; consider pharmacokinetic interactions when restarting therapy.

**Dosage adjustment with estrogen-containing hormonal contraceptives:** Follow initial lamotrigine dosing guidelines, maintenance dose should be adjusted as follows, based on concomitant medications:

- Patients taking concomitant carbamazepine, phenytoin, phenobarbital, primidone or rifampin: No dosing adjustment required
- Patients **not** taking concomitant carbamazepine, phenytoin, phenobarbital, primidone or rifampin: Lamotrigine maintenance dose may need increased by twofold over target dose. If already taking a stable dose of lamotrigine and starting contraceptive, maintenance dose may need increased by twofold. Dose increases should start when contraceptive is started and titrated to clinical response increasing no more rapidly than 50-100 mg daily every week. Gradual increases of lamotrigine plasma levels may occur during the inactive “pill-free” week and will be greater when dose increases are made the week before. If increased adverse events consistently occur during “pill-free” week, overall maintenance dose adjustments may be required. When discontinuing estrogen-containing hormonal contraceptive, dose of lamotrigine may need decreased by as much as 50%; do not decrease by more than 25% of total daily dose over a 2-week period unless clinical response or plasma levels indicate otherwise. Dose adjustments during “pill-free” week are not recommended.

**Renal Impairment:**
Decreased maintenance dosage may be effective in patients with significant renal impairment; has not been adequately studied; use with caution.

**Hepatic Impairment:**
**U.S. labeling:**
- Mild impairment: No adjustment required
- Moderate-to-severe impairment without ascites: Decrease initial, escalation, and maintenance doses by ~25%; adjust according to clinical response and tolerance.
- Moderate-to-severe impairment with ascites: Decrease initial, escalation, and maintenance doses by ~50%; adjust according to clinical response and tolerance.

**Canadian labeling:**
- Mild and moderate impairment (Child-Pugh classes A and B): Reduce initial, escalation, and maintenance dosing by ~50%; adjust according to clinical response and tolerance.
- Severe impairment (Child-Pugh class C): Reduce initial, escalation, and maintenance dosing by ~75%; adjust according to clinical response and tolerance.

**Common side effect:** Gastrointestinal: Nausea (7% to 14%)

**Pregnancy Risk Factor:** C