# INDICATIONS AND USAGE

Lamotrigine tablets USP, 600 mg, are indicated for the following conditions:

## Epilepsy

- Monotherapy in patients aged 16 years and older:
  - Partial-onset seizures.
  - Generalized tonic-clonic seizures.

- Adjunctive therapy in patients aged 16 years and older:
  - Partial-onset seizures.
  - Generalized tonic-clonic seizures.
  - Myoclonic seizures.
  - Absence seizures.

## Bipolar Disorder

- Maintenance therapy in adults and children aged 12 years and older:
  - Prospective, randomized, double-blind, placebo-controlled trials have not been conducted in patients aged 12 to 17 years.

## Dose and Administration

**Adults and Children Ages 12 Years and Older**

- **Dosing Regimen**
  - The initial dose for adults and children ages 12 years and older is 25 mg once or twice daily, with an increase every week to a maximum of 150 mg once or twice daily. The maximum dose is 300 mg once or twice daily.
  - The maintenance dose depends on the type of seizure and response to treatment. See Table 1.

## Special Populations

### Geriatric Use

- The safety and effectiveness of lamotrigine tablets USP have not been established in patients aged 65 years and older or younger than 18 years.

### Pediatric Use

- The safety and effectiveness of lamotrigine tablets USP have not been established in pediatric patients.

## Clinical Pharmacology

**Drug Interactions**

- **Valproate**
  - There is evidence that the inclusion of valproate in a multidrug regimen increases the risk of serious, potentially life-threatening rash in adults. In patients who used valproate concomitantly for epilepsy, 1.2% (6 of 482) experienced a serious rash compared to 0.005% in patients with refractory epilepsy. Consequently, whether these figures are reassuring or not possible to predict which rashes will prove to be serious is not possible to predict which rashes will prove to be serious is not possible to predict which rashes will prove to be serious.

**Drug Lactation**

- The decision to discontinue breastfeeding should be based on a consideration of the benefits of the drug and the possible adverse effects from both lamotrigine and its potential effects on the infant.

## Adverse Reactions

**Placebo-Controlled Trials**

- In adults with epilepsy, the incidences of adverse reactions were:
  - **Allergic**: Rash, including bullous or toxic epidermal necrolysis, and angioedema
  - **Neurologic**: Seizures, emotional lability, mood changes
  - **Central Nervous System**: Somnolence, disorientation, dizziness
  - **Respiratory**: Cough, pharyngitis
  - **Skin**: Pruritus
  - **Metabolic**: Hyperglycemia, hypoglycemia
  - **Gastrointestinal**: Nausea, vomiting, diarrhea, constipation

**Adjunctive Treatment**

- In children aged 2 to 12 years with epilepsy, the incidence of adverse reactions was:
  - **Allergic**: Rash, including bullous or toxic epidermal necrolysis, and angioedema
  - **Neurologic**: Seizures, emotional lability, mood changes
  - **Central Nervous System**: Somnolence, disorientation, dizziness
  - **Respiratory**: Cough, pharyngitis
  - **Skin**: Pruritus
  - **Metabolic**: Hyperglycemia, hypoglycemia
  - **Gastrointestinal**: Nausea, vomiting, diarrhea, constipation

**Withdrawal Seizures**

- Withdrawal seizures were observed in an adult patient who was tapered on lamotrigine and whose baseline seizure control had worsened. In a randomized controlled trial of adults with partial-onset seizures, 2 patients experienced seizures shortly after abrupt withdrawal of lamotrigine.

**Maintenance Seizures**

- In a group of adults with refractory secondarily generalized tonic-clonic seizures, 2 patients experienced seizures shortly after abrupt withdrawal of lamotrigine.

**Risk of Seizure Recurrence**

- In a randomized controlled trial of adults with partial-onset seizures, 2 patients experienced seizures shortly after abrupt withdrawal of lamotrigine.

**Unplanned Discontinuation of Treatment**

- Approximately 10% of the 420 adult patients who received SUBVENITE as monotherapy in premarketing clinical trials discontinued treatment due to adverse reactions.

**Drug-Drug Interactions**

- **Lamotrigine and Other Antiepileptic Drugs**
  - There are no data available on the effects of concomitant use of SUBVENITE with other antiepileptic drugs.

**Drug-Hormone Contraceptive Preparations and Hormone Replacement Therapy**

- Hormone replacement therapy is generally contra-indicated in women with epilepsy to reduce the risk of a serious, potentially life-threatening rash.

**Other Contraindications**

- **Hypersensitivity to the drug or its ingredients.** (Boxed Warning, 4)

## Dosage and Administration

**Epilepsy—Monotherapy in Patients Aged 16 Years and Older:**

- **Initial Dose:** 25 mg once or twice daily.
- **Maintenance Dose:** Depending on the type of seizure and response to treatment.

**Epilepsy—Adjunctive Therapy in Patients Aged 16 Years and Older:**

- **Adjunctive Therapy:** SUBVENITE can be administered in 1 or 2 divided doses. In 2 divided doses, rounded

**Bipolar Disorder—Maintenance Therapy in Adults:**

- **Initial Dose:** 25 mg once or twice daily.
- **Maintenance Dose:** Depending on the response to treatment.

**Geriatric Use:**

- The safety and effectiveness of lamotrigine tablets USP have not been established in patients aged 65 years and older.

**Pediatric Use:**

- The safety and effectiveness of lamotrigine tablets USP have not been established in pediatric patients.

**Special Populations:**

- The safety and effectiveness of lamotrigine tablets USP have not been established in patients aged 18 years and younger.

**Clinical Pharmacology (12.3):**

- lamotrigine is metabolized by O-dealkylation to 5,6-epoxide lamotrigine, which is further oxidized to an inactive glucuronide metabolite. The value of monitoring plasma concentrations of lamotrigine in patients treated with SUBVENITE has not been established. Because of the presence of significant interindividual variability in the clearance of lamotrigine, patients should be monitored for signs of toxicity.

**Drug Interactions: Valproate:**

- Valproate reduces the clearance of lamotrigine, the dosage of SUBVENITE in the presence of valproate is less than half of that recommended for monotherapy. Therefore, the initial dose for patients receiving valproate is 50 mg once or twice daily. In patients receiving valproate and lamotrigine for partial-onset seizures, the relative risk of serious, potentially life-threatening rash was 2.3 times higher than in patients receiving monotherapy with either drug.

**Drug Interactions: Other Antiepileptic Drugs:**

- The clinical significance of lamotrigine interactions with other antiepileptic drugs has not been established.

**Drug Interactions: Oral Contraceptives and Protease Inhibitors:**

- The potential for inhibition of lamotrigine glucuronidation by protease inhibitors is expected to be small. However, because the metabolism of lamotrigine is not saturable, the potential clinical significance of the interaction is unclear. The combination of lamotrigine with protease inhibitors is not recommended.

**Drug Interactions: Measuring Lamotrigine Concentrations:**

- Because of the high interindividual variability in the clearance of lamotrigine, it is not necessary to measure plasma concentrations of lamotrigine in patients treated with SUBVENITE.

**Drug Interactions: Monitoring Plasma Concentrations:**

- Because of the high interindividual variability in the clearance of lamotrigine, it is not necessary to monitor plasma concentrations of lamotrigine in patients treated with SUBVENITE.

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The effects of lamotrigine on valproate concentrations: preparations containing 30 mcg approximately 50%.

A Poison Control Center should be contacted for information on the management of overdosage of SUBVENITE.

Concomitant Drug SUBVENITE or Concomitant Drug Clinical Comment

Lennox-Gastaut syndrome, and PGTC seizures. Taking SUBVENITE (n = 87) and were twice as common compared with patients taking placebo (n = 86) were influenza (SUBVENITE 8%, placebo 4%).

Safety and efficacy of SUBVENITE for the maintenance treatment of bipolar disorder were not established in a double-blind, randomized clinical trial. In a study of 200 patients with bipolar disorder, the median time to occurrence of a mood episode (Figure 1) was 10 months (range: 1 to 24 months) for patients receiving 200 mg/day of lamotrigine, and 3 months (range: 0.5 to 24 months) for patients receiving 400 mg/day of lamotrigine. The median time to occurrence of a mood episode for patients receiving placebo was 3 months (range: 0.5 to 12 months). The primary efficacy variable was the proportion of patients who had a delay of at least 4 continuous weeks, including at least the final week on monotherapy with lamotrigine, in the time to occurrence of a mood episode. The secondary efficacy variable was the proportion of patients who had a delay of at least 4 continuous weeks, including at least the final week on monotherapy with lamotrigine, in the time to occurrence of a mood episode who also had a decrease in the severity of a mood episode. The primary efficacy variable was met in the 200-mg/day dose group, but not in the 400-mg/day dose group. The secondary efficacy variable was met in both the 200-mg/day and 400-mg/day dose groups. In the primary efficacy variable, the proportion of patients who had a delay of at least 4 continuous weeks, including at least the final week on monotherapy with lamotrigine, in the time to occurrence of a mood episode was significantly greater for patients receiving 200 mg/day of lamotrigine than for patients receiving placebo (p = 0.006). In the secondary efficacy variable, the proportion of patients who had a delay of at least 4 continuous weeks, including at least the final week on monotherapy with lamotrigine, in the time to occurrence of a mood episode and a decrease in the severity of a mood episode was significantly greater for patients receiving 200 mg/day of lamotrigine than for patients receiving placebo (p = 0.006).

The effects of doses of lamotrigine other than 300 mg/day have not been systematically evaluated in controlled clinical trials. In a study of 200 patients with bipolar disorder, the median time to occurrence of a mood episode was 10 months (range: 1 to 24 months) for patients receiving 200 mg/day of lamotrigine, and 3 months (range: 0.5 to 24 months) for patients receiving 400 mg/day of lamotrigine. The median time to occurrence of a mood episode for patients receiving placebo was 3 months (range: 0.5 to 12 months). The primary efficacy variable was the proportion of patients who had a delay of at least 4 continuous weeks, including at least the final week on monotherapy with lamotrigine, in the time to occurrence of a mood episode. The secondary efficacy variable was the proportion of patients who had a delay of at least 4 continuous weeks, including at least the final week on monotherapy with lamotrigine, in the time to occurrence of a mood episode who also had a decrease in the severity of a mood episode. The primary efficacy variable was met in the 200-mg/day dose group, but not in the 400-mg/day dose group. The secondary efficacy variable was met in both the 200-mg/day and 400-mg/day dose groups. In the primary efficacy variable, the proportion of patients who had a delay of at least 4 continuous weeks, including at least the final week on monotherapy with lamotrigine, in the time to occurrence of a mood episode was significantly greater for patients receiving 200 mg/day of lamotrigine than for patients receiving placebo (p = 0.006). In the secondary efficacy variable, the proportion of patients who had a delay of at least 4 continuous weeks, including at least the final week on monotherapy with lamotrigine, in the time to occurrence of a mood episode and a decrease in the severity of a mood episode was significantly greater for patients receiving 200 mg/day of lamotrigine than for patients receiving placebo (p = 0.006).

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