| Outcome | Once Daily plus RETROVIR plus Efavirenz (n = 278) | Twice Daily plus RETROVIR plus Efavirenz (n = 276) |
|---|---|---|
| Responder[a] | 67% | 65% |
| Virologic failure[b] | 8% | 8% |
| Discontinued due to clinical progression | <1% | 0% |
| Discontinued due to adverse events | 6% | 12% |
| Discontinued due to other reasons[c] | 18% | 14% |

[a] Achieved confirmed plasma HIV-1 RNA <400 copies/mL and maintained through 48 weeks.

[b] Achieved suppression but rebounded by Week 48, discontinued due to virologic failure, insufficient viral response according to the investigator, or never suppressed through Week 48.

[c] Includes consent withdrawn, lost to followup, protocol violation, data outside the study-defined schedule, and randomized but never initiated treatment.

The proportions of patients with HIV-1 RNA <50 copies/mL (via Roche Ultrasensitive assay) through Week 48 were 61% for patients receiving EPIVIR 300 mg once daily and 63% for patients receiving EPIVIR 150 mg twice daily. Median increases in CD4+ cell counts were 144 cells/$mm^3$ at Week 48 in patients receiving EPIVIR 300 mg once daily and 146 cells/$mm^3$ for patients receiving EPIVIR 150 mg twice daily.

A small, randomized, open-label pilot study, EPV40001, was conducted in Thailand. A total of 159 treatment-naive adult patients (male 32%, Asian 100%, median age 30 years, baseline median CD4+ cell count 380 cells/$mm^3$, median plasma HIV-1 RNA 4.8 $\log_{10}$ copies/mL) were enrolled. Two of the treatment arms in this study provided a comparison between lamivudine 300 mg once daily (n = 54) and lamivudine 150 mg twice daily (n = 52), each in combination with zidovudine 300 mg twice daily and abacavir 300 mg twice daily. In intent-to-treat analyses of 48-week data, the proportions of patients with HIV-1 RNA below 400 copies/mL were 61% (33/54) in the group randomized to once-daily lamivudine and 75% (39/52) in the group randomized to receive all 3 drugs twice daily; the proportions with HIV-1 RNA below 50 copies/mL were 54% (29/54) in the once-daily lamivudine group and 67% (35/52) in the all-twice-daily group; and the median increases in CD4+ cell counts were 166 cells/$mm^3$ in the once-daily lamivudine group and 216 cells/$mm^3$ in the all-twice-daily group.

### 14.2 Pediatric Patients

Clinical Endpoint Study: ACTG300 was a multi-center, randomized, double-blind study that provided for comparison of EPIVIR plus RETROVIR (zidovudine) with didanosine monotherapy. A total of 471 symptomatic, HIV-1-infected therapy-naive (≤56 days of antiretroviral therapy) pediatric patients were enrolled in these 2 treatment arms. The median age was 2.7 years (range: 6 weeks to 14 years), 58% were female, and 86% were non-Caucasian. The mean baseline CD4+ cell count was 868 cells/$mm^3$ (mean: 1,060 cells/$mm^3$ and range: 0 to 4,650 cells/$mm^3$ for patients ≤5 years of age; mean: 419 cells/$mm^3$ and range: 0 to 1,555 cells/$mm^3$ for patients >5 years of age) and the mean baseline plasma HIV-1 RNA was 5.0 $\log_{10}$ copies/mL. The median duration on study was 10.1 months for the patients receiving EPIVIR plus RETROVIR and 9.2 months for patients receiving didanosine monotherapy. Results are summarized in Table 10.

**Table 10. Number of Patients (%) Reaching a Primary Clinical Endpoint (Disease Progression or Death)**

| Endpoint | EPIVIR plus RETROVIR (n = 236) | Didanosine (n = 235) |
|---|---|---|
| HIV disease progression or death (total) | 15 (6.4%) | 37 (15.7%) |
| Physical growth failure | 7 (3.0%) | 6 (2.6%) |

| | | |
|---|---|---|
| Central nervous system deterioration | 4 (1.7%) | 12 (5.1%) |
| CDC Clinical Category C | 2 (0.8%) | 8 (3.4%) |
| Death | 2 (0.8%) | 11 (4.7%) |

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### EPIVIR Scored Tablets, 150 mg

White, diamond-shaped, scored, film-coated tablets debossed with "GX CJ7" on both sides.

Bottle of 60 tablets (NDC 0173-0470-01) with child-resistant closure.

### EPIVIR Tablets, 300 mg

Gray, modified diamond-shaped, film-coated tablets engraved with "GX EJ7" on one side and plain on the reverse side.

Bottle of 30 tablets (NDC 0173-0714-00) with child-resistant closure.

Recommended Storage:

Store EPIVIR Tablets at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

### EPIVIR Oral Solution, 10 mg/mL

A clear, colorless to pale yellow, strawberry-banana-flavored liquid, contains 10 mg of lamivudine in each 1 mL.

Plastic bottle of 240 mL (NDC 0173-0471-00) with child-resistant closure. This product does not require reconstitution.

Recommended Storage:

Store in tightly closed bottles at 25°C (77°F) [see USP Controlled Room Temperature].

## 17 PATIENT COUNSELING INFORMATION

### 17.1 Advice for the Patient

Information About Therapy With EPIVIR: EPIVIR is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using EPIVIR. Patients should be advised that the use of EPIVIR has not been shown to reduce the risk of transmission of HIV-1 to others through sexual contact or blood contamination.

Patients should be advised that the long-term effects of EPIVIR are unknown at this time.

Patients should be advised of the importance of taking EPIVIR with combination therapy on a regular dosing schedule and to avoid missing doses.

EPIVIR should not be coadministered with drugs containing lamivudine or emtricitabine, including COMBIVIR (lamivudine/zidovudine) Tablets, EPZICOM (abacavir sulfate and lamivudine) Tablets, TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine), ATRIPLA (efavirenz, emtricitabine, and tenofovir), EMTRIVA (emtricitabine) or TRUVADA (emtricitabine and tenofovir) *[see Warnings and Precautions (5.3)]*.

Redistribution/Accumulation of Body Fat: Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, including EPIVIR, and that the cause and long-term health effects of these conditions are not known at this time *[see Warnings and Precautions (5.7)]*.

Differences in Formulations of EPIVIR: Patients should be advised that EPIVIR Tablets and Oral Solution contain a higher dose of the same active ingredient (lamivudine) as EPIVIR-HBV Tablets and Oral Solution. If a decision is made to include lamivudine in the HIV-1 treatment regimen of a patient co-infected with HIV-1 and HBV, the formulation and dosage of lamivudine in EPIVIR (not EPIVIR-HBV) should be used *[see Warnings and Precautions (5.2)]*.

Co-infection With HIV-1 and HBV: Patients co-infected with HIV-1 and HBV should be informed that deterioration of liver disease has occurred in some cases when treatment with lamivudine was discontinued. Patients should be advised to discuss any changes in regimen with their physician *[see Warnings and Precautions (5.2)]*.

Risk of Pancreatitis: Parents or guardians should be advised to monitor pediatric patients for signs and symptoms of pancreatitis *[see Warnings and Precautions (5.5)]*.

Sucrose Content of EPIVIR Oral Solution: Diabetic patients should be advised that each 15-mL dose of EPIVIR Oral Solution contains 3 grams of sucrose *[see Description (11)]*.



GlaxoSmithKline
Research Triangle Park, NC 27709

Manufactured under agreement from
**Shire Pharmaceuticals Group plc**
Basingstoke, UK



**PRINCIPAL DISPLAY PANEL**

**NDC 0173-0471-00**

**EPIVIR®**

**(lamivudine)**

**ORAL SOLUTION**

**10 mg/mL**

**ALCOHOL FREE**

**$R_x$ only**

**240 mL**

See prescribing information for dosage information.

Store in tightly closed bottles at 25°C (77°F) (see USP Controlled Room Temperature).

GlaxoSmithKline

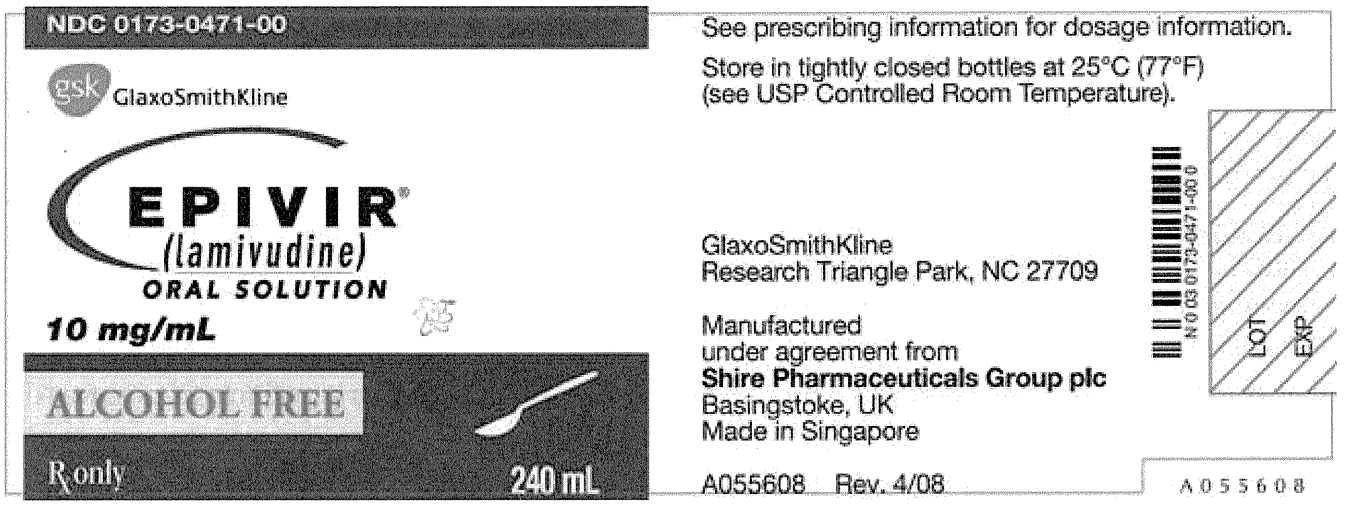
Research Triangle Park, NC 27709

Manufactured under agreement from **Shire Pharmaceuticals Group plc**

Basingstoke, UK

Made in Singapore

A055608 Rev. 4/08




**PRINCIPAL DISPLAY PANEL**

**NDC 0173-0470-01**

**EPIVIR®**

**(lamivudine)**

**TABLETS**

**150 mg**

**$R_x$ only**

**60 Tablets**

Each scored tablet contains 150 mg of lamivudine.

See prescribing information for Dosage and Administration.

Store at 25ºC (77ºF); excursions permitted to 15º to 30ºC (59º to 86ºF) [see USP Controlled Room Temperature].

Manufactured under agreement from **Shire Pharmaceuticals Group plc**

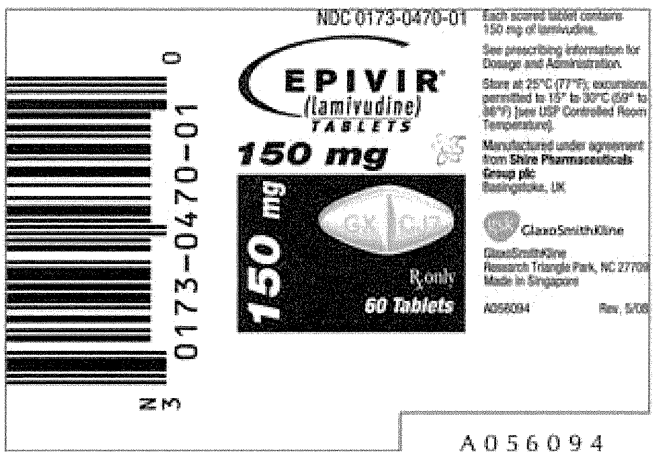
Basingstoke, UK

GlaxoSmithKline

Research Triangle Park, NC 27709

Made in Singapore

A056094 Rev.5/08




**PRINCIPAL DISPLAY PANEL**

**NDC 0173-0714-00**

**EPIVIR®**

**(lamivudine)**

**TABLETS**

**300 mg**

**$R_x$ only**

**30 Tablets**

Each scored tablet contains 300 mg of lamivudine.

See prescribing information for Dosage and Administration.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Manufactured under agreement from **Shire Pharmaceuticals Group plc**

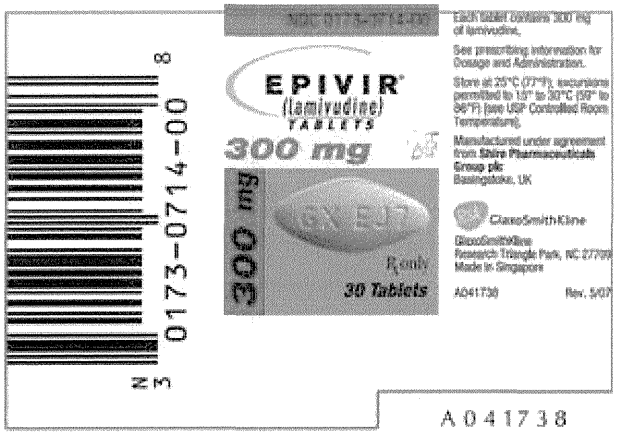
Basingstoke, UK

GlaxoSmithKline

Research Triangle Park, NC 27709

Made in Singapore

A041738 Rev.5/07




## EPIVIR

lamivudine tablet, film coated

| Product Information | | | |
|---|---|---|---|
| **Product Type** | HUMAN PRESCRIPTION DRUG LABEL | **Item Code (Source)** | NDC:0173-0470 |
| **Route of Administration** | ORAL | **DEA Schedule** | |

| Active Ingredient/Active Moiety | | |
|---|---|---|
| **Ingredient Name** | **Basis of Strength** | **Strength** |
| **LAMIVUDINE** (LAMIVUDINE) | LAMIVUDINE | 150 mg |

| Inactive Ingredients | |
|---|---|
| **Ingredient Name** | **Strength** |
| HYPROMELLOSES | |
| MAGNESIUM STEARATE | |
| CELLULOSE, MICROCRYSTALLINE | |
| POLYETHYLENE GLYCOL | |
| POLYSORBATE 80 | |
| SODIUM STARCH GLYCOLATE TYPE A POTATO | |
| TITANIUM DIOXIDE | |

| Product Characteristics | | | |
|---|---|---|---|
| **Color** | WHITE | **Score** | 2 pieces |
| **Shape** | DIAMOND | **Size** | 14mm |
| **Flavor** | | **Imprint Code** | GX;CJ7 |
| **Contains** | | | |

| Packaging | | | | |
|---|---|---|---|---|
| **#** | **Item Code** | **Package Description** | **Marketing Start Date** | **Marketing End Date** |
| **1** | NDC:0173-0470-01 | 60 in 1 BOTTLE | | |

## Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|---|---|---|---|
| NDA | NDA020564 | 11/21/1995 | 06/16/2015 |

# EPIVIR

lamivudine solution

| Product Information | | | |
|---|---|---|---|
| **Product Type** | HUMAN PRESCRIPTION DRUG LABEL | **Item Code (Source)** | NDC:0173-0471 |
| **Route of Administration** | ORAL | **DEA Schedule** | |

| Active Ingredient/Active Moiety | | |
|---|---|---|
| **Ingredient Name** | **Basis of Strength** | **Strength** |
| **LAMIVUDINE** (LAMIVUDINE) | LAMIVUDINE | 10 mg in 1 mL |

| Inactive Ingredients | |
|---|---|
| **Ingredient Name** | **Strength** |
| ANHYDROUS CITRIC ACID | |
| METHYLPARABEN | |

| | |
|---|---|
| **PROPYLENE GLYCOL** | |
| **PROPYLPARABEN** | |
| **TRISODIUM CITRATE DIHYDRATE** | |
| **SUCROSE** | |

### Product Characteristics

| | | | |
|---|---|---|---|
| **Color** | YELLOW (colorless to pale yellow) | **Score** | |
| **Shape** | | **Size** | |
| **Flavor** | STRAWBERRY (strawberry-banana) | **Imprint Code** | |
| **Contains** | | | |

### Packaging

| # | Item Code | Package Description | Marketing Start Date | Marketing End Date |
|---|---|---|---|---|
| **1** | NDC:0173-0471-00 | 240 mL in 1 BOTTLE | | |

## Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|---|---|---|---|
| NDA | NDA020596 | 11/21/1995 | 07/31/2012 |

# EPIVIR

lamivudine tablet, film coated

### Product Information

| | | | |
|---|---|---|---|
| **Product Type** | HUMAN PRESCRIPTION DRUG LABEL | **Item Code (Source)** | NDC:0173-0714 |
| **Route of Administration** | ORAL | **DEA Schedule** | |

### Active Ingredient/Active Moiety

| Ingredient Name | Basis of Strength | Strength |
|---|---|---|
| **LAMIVUDINE** (LAMIVUDINE) | LAMIVUDINE | 300 mg |

### Inactive Ingredients

| Ingredient Name | Strength |
|---|---|
| **FERRIC OXIDE BLACK** | |
| **HYPROMELLOSES** | |
| **MAGNESIUM STEARATE** | |
| **CELLULOSE, MICROCRYSTALLINE** | |
| **POLYETHYLENE GLYCOL** | |
| **POLYSORBATE 80** | |
| **SODIUM STARCH GLYCOLATE TYPE A POTATO** | |
| **TITANIUM DIOXIDE** | |

| Product Characteristics | | | |
|---|---|---|---|
| **Color** | GRAY | **Score** | no score |
| **Shape** | DIAMOND | **Size** | 17mm |
| **Flavor** | | **Imprint Code** | GX;EJ7 |
| **Contains** | | | |

**Packaging**

| # | Item Code | Package Description | Marketing Start Date | Marketing End Date |
|---|---|---|---|---|
| **1** | NDC:0173-0714-00 | 30 in 1 BOTTLE | | |

## Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|---|---|---|---|
| NDA | NDA020564 | 09/25/2002 | 06/09/2013 |

## Labeler - GlaxoSmithKline LLC (167380711)

Revised: 1/2011 GlaxoSmithKline LLC

**LAMICTAL- lamotrigine tablet**
**LAMICTAL- lamotrigine tablet, chewable**
**LAMICTAL ODT- lamotrigine tablet, orally disintegrating**
**LAMICTAL- lamotrigine**
**LAMICTAL ODT- lamotrigine**
**GlaxoSmithKline LLC**

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**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use LAMICTAL safely and effectively. See full prescribing information for LAMICTAL.**
**LAMICTAL (lamotrigine) Tablets**
**LAMICTAL (lamotrigine) Chewable Dispersible Tablets**
**LAMICTAL ODT (lamotrigine) Orally Disintegrating Tablets**
**Initial U.S. Approval: 1994**

**WARNING: SERIOUS SKIN RASHES**

***See full prescribing information for complete boxed warning.***

**Cases of life-threatening serious rashes, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and/or rash-related death, have been caused by LAMICTAL. The rate of serious rash is greater in pediatric patients than in adults. Additional factors that may increase the risk of rash include (5.1):**

- **coadministration with valproate**
- **exceeding recommended initial dose of LAMICTAL**
- **exceeding recommended dose escalation of LAMICTAL**

**Benign rashes are also caused by LAMICTAL; however, it is not possible to predict which rashes will prove to be serious or life threatening. LAMICTAL should be discontinued at the first sign of rash, unless the rash is clearly not drug related. (5.1)**

## INDICATIONS AND USAGE

LAMICTAL is an antiepileptic drug (AED) indicated for: (1)
**Epilepsy—adjunctive therapy in patients ≥2 years of age:** (1.1) (1)

- partial seizures
- primary generalized tonic-clonic seizures
- generalized seizures of Lennox-Gastaut syndrome

**Epilepsy—monotherapy in patients ≥16 years of age:** conversion to monotherapy in patients with partial seizures who are receiving treatment with carbamazepine, phenobarbital, phenytoin, primidone, or valproate as the single AED. (1.1) (1)
**Bipolar Disorder in patients ≥18 years of age:** maintenance treatment of Bipolar I Disorder to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy. (1.2) (1)

## DOSAGE AND ADMINISTRATION

- Dosing is based on concomitant medications, indication, and patient age. (2.2, 2.4)
- To avoid an increased risk of rash, the recommended initial dose and subsequent dose escalations should not be exceeded. LAMICTAL Starter Kits and LAMICTAL ODT Patient Titration Kits are available for the first 5 weeks of treatment. (2.1, 16)
- Do not restart LAMICTAL in patients who discontinued due to rash unless the potential benefits clearly outweigh the risks. (2.1)
- Adjustments to maintenance doses will in most cases be required in patients starting or stopping estrogen-containing oral contraceptives. (2.1, 5.8)
- LAMICTAL should be discontinued over a period of at least 2 weeks (approximately 50% reduction per week). (2.1, 5.9)

**Epilepsy** (2)

- Adjunctive therapy—See Table 1 for patients >12 years of age and Tables 2 and 3 for patients 2 to 12 years. (2.2)

- Conversion to monotherapy—See Table 4. (2.3)

**Bipolar Disorder:** See Tables 5 and 6. (2.4) (2)

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**DOSAGE FORMS AND STRENGTHS**

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**Tablets:** 25 mg, 100 mg, 150 mg, and 200 mg scored. (3.1, 16) (3)
**Chewable Dispersible Tablets:** 2 mg, 5 mg, and 25 mg. (3.2, 16) (3)
**Orally Disintegrating Tablets**: 25 mg, 50 mg, 100 mg, and 200 mg. (3.3, 16) (3)

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**CONTRAINDICATIONS**

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

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**WARNINGS AND PRECAUTIONS**

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- Life-threatening serious rash and/or rash-related death may result. (Boxed Warning, 5.1)
- Fatal or life-threatening hypersensitivity reaction: Multiorgan hypersensitivity reactions, also known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), may be fatal or life threatening. Early signs may include rash, fever, and lymphadenopathy. These reactions may be associated with other organ involvement, such as hepatitis, hepatic failure, blood dyscrasias, or acute multiorgan failure. LAMICTAL should be discontinued if alternate etiology for this reaction is not found. (5.2)
- Blood dyscrasias (e.g., neutropenia, thrombocytopenia, pancytopenia): May occur, either with or without an associated hypersensitivity syndrome. (5.3)
- Suicidal behavior and ideation. (5.4)
- Clinical worsening, emergence of new symptoms, and suicidal ideation/behaviors may be associated with treatment of bipolar disorder. Patients should be closely monitored, particularly early in treatment or during dosage changes. (5.5)
- Aseptic meningitis reported in pediatric and adult patients. (5.6)
- Medication errors involving LAMICTAL have occurred. In particular the names LAMICTAL or lamotrigine can be confused with names of other commonly used medications. Medication errors may also occur between the different formulations of LAMICTAL. (3.4, 5.7, 16, 17.10)

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**ADVERSE REACTIONS**

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- Most common adverse reactions (incidence ≥10%) in adult epilepsy clinical studies were dizziness, headache, diplopia, ataxia, nausea, blurred vision, somnolence, rhinitis, and rash. Additional adverse reactions (incidence ≥10%) reported in children in epilepsy clinical studies included vomiting, infection, fever, accidental injury, pharyngitis, abdominal pain, and tremor. (6.1)
- Most common adverse reactions (incidence >5%) in adult bipolar clinical studies were nausea, insomnia, somnolence, back pain, fatigue, rash, rhinitis, abdominal pain, and xerostomia. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

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**DRUG INTERACTIONS**

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- Valproate increases lamotrigine concentrations more than 2-fold. (7, 12.3)
- Carbamazepine, phenytoin, phenobarbital, and primidone decrease lamotrigine concentrations by approximately 40%. (7, 12.3)
- Oral estrogen-containing contraceptives and rifampin also decrease lamotrigine concentrations by approximately 50%. (7, 12.3)

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**USE IN SPECIFIC POPULATIONS**

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- Hepatic impairment: Dosage adjustments required. (2.1)
- Healthcare professionals can enroll patients in the Lamotrigine Pregnancy Registry (1-800-336-2176). Patients can enroll themselves in the North American Antiepileptic Drug Pregnancy Registry (1-888-233-2334). (8.1)
- Efficacy of LAMICTAL, used as adjunctive treatment for partial seizures, was not demonstrated in a small, randomized, double-blind, placebo-controlled study in very young pediatric patients (1 to 24 months). (8.4)

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**

**Revised: 9/2012**

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**FULL PRESCRIBING INFORMATION: CONTENTS***

* Sections or subsections omitted from the full prescribing information are not listed.

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**FULL PRESCRIBING INFORMATION**

**WARNING: SERIOUS SKIN RASHES**

**LAMICTAL® can cause serious rashes requiring hospitalization and discontinuation of treatment. The incidence of these rashes, which have included Stevens-Johnson syndrome, is approximately 0.8% (8 per 1,000) in pediatric patients (2 to 16 years of age) receiving LAMICTAL as adjunctive therapy for epilepsy and 0.3% (3 per 1,000) in adults on adjunctive therapy for epilepsy. In clinical trials of bipolar and other mood disorders, the rate of serious rash was 0.08% (0.8 per 1,000) in adult patients receiving LAMICTAL as initial monotherapy and 0.13% (1.3 per 1,000) in adult patients receiving LAMICTAL as adjunctive therapy. In a prospectively followed cohort of 1,983 pediatric patients (2 to 16 years of age) with epilepsy taking adjunctive LAMICTAL, there was 1 rash-related death. In worldwide postmarketing experience, rare cases of toxic epidermal necrolysis and/or rash-related death have been reported in adult and pediatric patients, but their numbers are too few to permit a precise estimate of the rate.**

**Other than age, there are as yet no factors identified that are known to predict the risk of occurrence or the severity of rash caused by LAMICTAL. There are suggestions, yet to be proven, that the risk of rash may also be increased by (1) coadministration of LAMICTAL with valproate (includes valproic acid and divalproex sodium), (2) exceeding the recommended initial dose of LAMICTAL, or (3) exceeding the recommended dose escalation for LAMICTAL. However, cases have occurred in the absence of these factors.**

**Nearly all cases of life-threatening rashes caused by LAMICTAL have occurred within 2 to 8 weeks of treatment initiation. However, isolated cases have occurred after prolonged treatment (e.g., 6 months). Accordingly, duration of therapy cannot be relied upon as means to predict the potential risk heralded by the first appearance of a rash.**

**Although benign rashes are also caused by LAMICTAL, it is not possible to predict reliably which rashes will prove to be serious or life threatening. Accordingly, LAMICTAL should ordinarily be discontinued at the first sign of rash, unless the rash is clearly not drug related. Discontinuation of treatment may not prevent a rash from becoming life threatening or permanently disabling or disfiguring *[see Warnings and Precautions (5.1)]*.**

## 1 INDICATIONS AND USAGE

### 1.1 Epilepsy

Adjunctive Therapy: LAMICTAL is indicated as adjunctive therapy for the following seizure types in patients ≥2 years of age:

- partial seizures
- primary generalized tonic-clonic seizures
- generalized seizures of Lennox-Gastaut syndrome

Monotherapy: LAMICTAL is indicated for conversion to monotherapy in adults (≥16 years of age) with partial seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single antiepileptic drug (AED).

Safety and effectiveness of LAMICTAL have not been established (1) as initial monotherapy; (2) for conversion to monotherapy from AEDs other than carbamazepine, phenytoin, phenobarbital, primidone, or valproate; or (3) for simultaneous conversion to monotherapy from 2 or more concomitant AEDs.

### 1.2 Bipolar Disorder

LAMICTAL is indicated for the maintenance treatment of Bipolar I Disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in adults (≥18 years of age) treated for acute mood episodes with standard therapy. The effectiveness of LAMICTAL in the acute treatment of mood episodes has not been established.

The effectiveness of LAMICTAL as maintenance treatment was established in 2 placebo-controlled trials in patients with Bipolar I Disorder as defined by DSM-IV *[see Clinical Studies (14.2)]*. The physician who elects to prescribe LAMICTAL for periods extending beyond 16 weeks should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 General Dosing Considerations

Rash: There are suggestions, yet to be proven, that the risk of severe, potentially life-threatening rash may be increased by (1) coadministration of LAMICTAL with valproate, (2) exceeding the recommended initial dose of LAMICTAL, or (3) exceeding the recommended dose escalation for LAMICTAL. However, cases have occurred in the absence of these factors *[see Boxed Warning]*. Therefore, it is important that the dosing recommendations be followed closely.

The risk of nonserious rash may be increased when the recommended initial dose and/or the rate of dose escalation of LAMICTAL is exceeded and in patients with a history of allergy or rash to other AEDs.

LAMICTAL Starter Kits and LAMICTAL® ODT™ Patient Titration Kits provide LAMICTAL at doses consistent with the recommended titration schedule for the first 5 weeks of treatment, based upon concomitant medications, for patients with epilepsy (>12 years of age) and Bipolar I Disorder (≥18 years of age) and are intended to help reduce the potential for rash. The use of LAMICTAL Starter Kits and LAMICTAL ODT Patient Titration Kits is recommended for appropriate patients who are starting or restarting LAMICTAL *[see How Supplied/Storage and Handling (16)]*.

It is recommended that LAMICTAL not be restarted in patients who discontinued due to rash associated with prior treatment with lamotrigine, unless the potential benefits clearly outweigh the risks. If the decision is made to restart a patient who has discontinued lamotrigine, the need to restart with the initial dosing recommendations should be assessed. The greater the interval of time since the previous dose, the greater consideration should be given to restarting with the initial dosing recommendations. If a patient has discontinued lamotrigine for a period of more than 5 half-lives, it is recommended that initial dosing recommendations and guidelines be followed. The half-life of lamotrigine is affected by other concomitant medications *[see Clinical Pharmacology (12.3)]*.

LAMICTAL Added to Drugs Known to Induce or Inhibit Glucuronidation: Drugs other than those listed in the Clinical Pharmacology section *[see Clinical Pharmacology (12.3)]* have not been systematically evaluated in combination with lamotrigine. Because lamotrigine is metabolized predominantly by glucuronic acid conjugation, drugs that are known to induce or inhibit glucuronidation may affect the apparent clearance of lamotrigine and doses of LAMICTAL may require adjustment based on clinical response.

Target Plasma Levels for Patients With Epilepsy or Bipolar Disorder: A therapeutic plasma concentration range has not been established for lamotrigine. Dosing of LAMICTAL should be based on therapeutic response *[see Clinical Pharmacology (12.3)]*.

Women Taking Estrogen-Containing Oral Contraceptives:*Starting LAMICTAL in Women Taking Estrogen-Containing Oral Contraceptives:* Although estrogen-containing oral contraceptives have been shown to increase the clearance of lamotrigine *[see Clinical Pharmacology (12.3)]*, no adjustments to the recommended dose-escalation guidelines for LAMICTAL should be necessary solely based on the use of estrogen-containing oral contraceptives. Therefore, dose escalation should follow the recommended guidelines for initiating adjunctive therapy with LAMICTAL based on the concomitant AED or other

concomitant medications (see Table 1 or Table 5). See below for adjustments to maintenance doses of LAMICTAL in women taking estrogen-containing oral contraceptives.

*Adjustments to the Maintenance Dose of LAMICTAL in Women Taking Estrogen-Containing Oral Contraceptives:*

*(1) Taking Estrogen-Containing Oral Contraceptives:* For women not taking carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin that induce lamotrigine glucuronidation *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*, the maintenance dose of LAMICTAL will in most cases need to be increased, by as much as 2-fold over the recommended target maintenance dose, to maintain a consistent lamotrigine plasma level *[see Clinical Pharmacology (12.3)]*.

*(2) Starting Estrogen-Containing Oral Contraceptives:* In women taking a stable dose of LAMICTAL and not taking carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin that induce lamotrigine glucuronidation *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*, the maintenance dose will in most cases need to be increased by as much as 2-fold to maintain a consistent lamotrigine plasma level. The dose increases should begin at the same time that the oral contraceptive is introduced and continue, based on clinical response, no more rapidly than 50 to 100 mg/day every week. Dose increases should not exceed the recommended rate (see Table 1 or Table 5) unless lamotrigine plasma levels or clinical response support larger increases. Gradual transient increases in lamotrigine plasma levels may occur during the week of inactive hormonal preparation ("pill-free" week), and these increases will be greater if dose increases are made in the days before or during the week of inactive hormonal preparation. Increased lamotrigine plasma levels could result in additional adverse reactions, such as dizziness, ataxia, and diplopia. If adverse reactions attributable to LAMICTAL consistently occur during the "pill-free" week, dose adjustments to the overall maintenance dose may be necessary. Dose adjustments limited to the "pill-free" week are not recommended. For women taking LAMICTAL in addition to carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin that induce lamotrigine glucuronidation *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*, no adjustment to the dose of LAMICTAL should be necessary.

*(3) Stopping Estrogen-Containing Oral Contraceptives:* For women not taking carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin that induce lamotrigine glucuronidation *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*, the maintenance dose of LAMICTAL will in most cases need to be decreased by as much as 50% in order to maintain a consistent lamotrigine plasma level. The decrease in dose of LAMICTAL should not exceed 25% of the total daily dose per week over a 2-week period, unless clinical response or lamotrigine plasma levels indicate otherwise *[see Clinical Pharmacology (12.3)]*. For women taking LAMICTAL in addition to carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin that induce lamotrigine glucuronidation *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*, no adjustment to the dose of LAMICTAL should be necessary.

Women and Other Hormonal Contraceptive Preparations or Hormone Replacement Therapy: The effect of other hormonal contraceptive preparations or hormone replacement therapy on the pharmacokinetics of lamotrigine has not been systematically evaluated. It has been reported that ethinylestradiol, not progestogens, increased the clearance of lamotrigine up to 2-fold, and the progestin-only pills had no effect on lamotrigine plasma levels. Therefore, adjustments to the dosage of LAMICTAL in the presence of progestogens alone will likely not be needed.

Patients With Hepatic Impairment: Experience in patients with hepatic impairment is limited. Based on a clinical pharmacology study in 24 patients with mild, moderate, and severe liver impairment *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*, the following general recommendations can be made. No dosage adjustment is needed in patients with mild liver impairment. Initial, escalation, and maintenance doses should generally be reduced by approximately 25% in patients with moderate and severe liver impairment without ascites and 50% in patients with severe liver impairment with ascites. Escalation and maintenance doses may be adjusted according to clinical response.

Patients With Renal Impairment: Initial doses of LAMICTAL should be based on patients' concomitant

medications (see Tables 1-3 or Table 5); reduced maintenance doses may be effective for patients with significant renal impairment *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*. Few patients with severe renal impairment have been evaluated during chronic treatment with LAMICTAL. Because there is inadequate experience in this population, LAMICTAL should be used with caution in these patients.

Discontinuation Strategy:*Epilepsy:* For patients receiving LAMICTAL in combination with other AEDs, a reevaluation of all AEDs in the regimen should be considered if a change in seizure control or an appearance or worsening of adverse reactions is observed.

If a decision is made to discontinue therapy with LAMICTAL, a step-wise reduction of dose over at least 2 weeks (approximately 50% per week) is recommended unless safety concerns require a more rapid withdrawal *[see Warnings and Precautions (5.9)]*.

Discontinuing carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin that induce lamotrigine glucuronidation should prolong the half-life of lamotrigine; discontinuing valproate should shorten the half-life of lamotrigine.

*Bipolar Disorder:* In the controlled clinical trials, there was no increase in the incidence, type, or severity of adverse reactions following abrupt termination of LAMICTAL. In clinical trials in patients with Bipolar Disorder, 2 patients experienced seizures shortly after abrupt withdrawal of LAMICTAL. However, there were confounding factors that may have contributed to the occurrence of seizures in these bipolar patients. Discontinuation of LAMICTAL should involve a step-wise reduction of dose over at least 2 weeks (approximately 50% per week) unless safety concerns require a more rapid withdrawal *[see Warnings and Precautions (5.9)]*.

### 2.2 Epilepsy – Adjunctive Therapy

This section provides specific dosing recommendations for patients greater than 12 years of age and patients 2 to 12 years of age. Within each of these age-groups, specific dosing recommendations are provided depending upon concomitant AED or other concomitant medications (Table 1 for patients greater than 12 years of age and Table 2 for patients 2 to 12 years of age). A weight-based dosing guide for patients 2 to 12 years of age on concomitant valproate is provided in Table 3.

Patients Over 12 Years of Age: Recommended dosing guidelines are summarized in Table 1.

**Table 1. Escalation Regimen for LAMICTAL in Patients Over 12 Years of Age With Epilepsy**

| | For Patients TAKING Valproate[a] | For Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone,[b] or Valproate[a] | For Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone[b] and NOT TAKING Valproate[a] |
|---|---|---|---|
| Weeks 1 and 2 | **25 mg every *other* day** | **25 mg every day** | **50 mg/day** |
| Weeks 3 and 4 | **25 mg every day** | **50 mg/day** | **100 mg/day** (in 2 divided doses) |
| Week 5 onwards to maintenance | Increase by 25 to 50 mg/day every 1 to 2 weeks | Increase by 50 mg/day every 1 to 2 weeks | Increase by 100 mg/day every 1 to 2 weeks. |
| Usual maintenance dose | **100 to 200 mg/day with valproate alone**<br>**100 to 400 mg/day with valproate and other drugs** | **225 to 375 mg/day** (in 2 divided doses) | **300 to 500 mg/day** (in 2 divided doses) |

| | | | |
|---|---|---|---|
| | **that induce glucuronidation** (in 1 or 2 divided doses) | | |

[a]Valproate has been shown to inhibit glucuronidation and decrease the apparent clearance of lamotrigine *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*.

[b]These drugs induce lamotrigine glucuronidation and increase clearance *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*. Other drugs that have similar effects include estrogen-containing oral contraceptives *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*. Dosing recommendations for oral contraceptives can be found in General Dosing Considerations *[see Dosage and Administration (2.1)]*. Patients on rifampin, or other drugs that induce lamotrigine glucuronidation and increase clearance, should follow the same dosing titration/maintenance regimen as that used with anticonvulsants that have this effect.

Patients 2 to 12 Years of Age: Recommended dosing guidelines are summarized in Table 2.

Smaller starting doses and slower dose escalations than those used in clinical trials are recommended because of the suggestion that the risk of rash may be decreased by smaller starting doses and slower dose escalations. Therefore, maintenance doses will take longer to reach in clinical practice than in clinical trials. It may take several weeks to months to achieve an individualized maintenance dose. Maintenance doses in patients weighing less than 30 kg, regardless of age or concomitant AED, may need to be increased as much as 50%, based on clinical response.

**The smallest available strength of LAMICTAL Chewable Dispersible Tablets is 2 mg, and only whole tablets should be administered. If the calculated dose cannot be achieved using whole tablets, the dose should be rounded down to the nearest whole tablet** *[see How Supplied/Storage and Handling (16) and Medication Guide]*.

**Table 2. Escalation Regimen for LAMICTAL in Patients 2 to 12 Years of Age With Epilepsy**

| | For Patients TAKING Valproate[a] | For Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone,[b] or Valproate[a] | For Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone[b] and NOT TAKING Valproate[a] |
|---|---|---|---|
| Weeks 1 and 2 | **0.15 mg/kg/day** in 1 or 2 divided doses, rounded down to the nearest whole tablet (see Table 3 for weight-based dosing guide) | **0.3 mg/kg/day** in 1 or 2 divided doses, rounded down to the nearest whole tablet | **0.6 mg/kg/day** in 2 divided doses, rounded down to the nearest whole tablet |
| Weeks 3 and 4 | **0.3 mg/kg/day** in 1 or 2 divided doses, rounded down to the nearest whole tablet (see Table 3 for weight-based dosing guide) | **0.6 mg/kg/day** in 2 divided doses, rounded down to the nearest whole tablet | **1.2 mg/kg/day** in 2 divided doses, rounded down to the nearest whole tablet |
| Week 5 onwards to maintenance | The dose should be increased every 1 to 2 weeks as follows: calculate 0.3 mg/kg/day, round this amount down to the nearest whole tablet, and add this | The dose should be increased every 1 to 2 weeks as follows: calculate 0.6 mg/kg/day, round this amount down to the nearest | The dose should be increased every 1 to 2 |

| | | | |
|---|---|---|---|
| | amount to the previously administered daily dose | whole tablet, and add this amount to the previously administered daily dose | weeks as follows: calculate 1.2 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily dose |
| Usual maintenance dose | **1 to 5 mg/kg/day**(maximum 200 mg/day in 1 or 2 divided doses)<br>**1 to 3 mg/kg/day**<br>with valproate alone | **4.5 to 7.5 mg/kg/day**<br>(maximum 300 mg/day in 2 divided doses) | **5 to 15 mg/kg/day**<br>(maximum 400 mg/day in 2 divided doses) |
| Maintenance dose in patients less than 30 kg | May need to be increased by as much as 50%, based on clinical response | May need to be increased by as much as 50%, based on clinical response | May need to be increased by as much as 50%, based on clinical response |

**Note: Only whole tablets should be used for dosing.**

[a]Valproate has been shown to inhibit glucuronidation and decrease the apparent clearance of lamotrigine *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*.

[b]These drugs induce lamotrigine glucuronidation and increase clearance *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*. Other drugs that have similar effects include estrogen-containing oral contraceptives *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*. Dosing recommendations for oral contraceptives can be found in General Dosing Considerations *[see Dosage and Administration (2.1)]*. Patients on rifampin, or other drugs that induce lamotrigine glucuronidation and increase clearance, should follow the same dosing titration/maintenance regimen as that used with anticonvulsants that have this effect.

**Table 3. The Initial Weight-Based Dosing Guide for Patients 2 to 12 Years of Age Taking Valproate (Weeks 1 to 4) With Epilepsy**

| If the patient's weight is | | Give this daily dose, using the most appropriate combination of LAMICTAL 2-mg and 5-mg tablets | |
|---|---|---|---|
| Greater than | And less than | Weeks 1 and 2 | Weeks 3 and 4 |
| 6.7 kg | 14 kg | 2 mg every *other* day | 2 mg every day |
| 14.1 kg | 27 kg | 2 mg every day | 4 mg every day |
| 27.1 kg | 34 kg | 4 mg every day | 8 mg every day |
| 34.1 kg | 40 kg | 5 mg every day | 10 mg every day |

Usual Adjunctive Maintenance Dose for Epilepsy: The usual maintenance doses identified in Tables 1 and 2 are derived from dosing regimens employed in the placebo-controlled adjunctive studies in which the efficacy of LAMICTAL was established. In patients receiving multidrug regimens employing

carbamazepine, phenytoin, phenobarbital, or primidone **without valproate**, maintenance doses of adjunctive LAMICTAL as high as 700 mg/day have been used. In patients receiving **valproate alone**, maintenance doses of adjunctive LAMICTAL as high as 200 mg/day have been used. The advantage of using doses above those recommended in Tables 1 through 4 has not been established in controlled trials.

### 2.3 Epilepsy – Conversion From Adjunctive Therapy to Monotherapy

The goal of the transition regimen is to effect the conversion to monotherapy with LAMICTAL under conditions that ensure adequate seizure control while mitigating the risk of serious rash associated with the rapid titration of LAMICTAL.

The recommended maintenance dose of LAMICTAL as monotherapy is 500 mg/day given in 2 divided doses.

To avoid an increased risk of rash, the recommended initial dose and subsequent dose escalations of LAMICTAL should not be exceeded *[see Boxed Warning]*.

Conversion From Adjunctive Therapy With Carbamazepine, Phenytoin, Phenobarbital, or Primidone to Monotherapy With LAMICTAL: After achieving a dose of 500 mg/day of LAMICTAL according to the guidelines in Table 1, the concomitant AED should be withdrawn by 20% decrements each week over a 4-week period. The regimen for the withdrawal of the concomitant AED is based on experience gained in the controlled monotherapy clinical trial.

Conversion From Adjunctive Therapy With Valproate to Monotherapy With LAMICTAL: The conversion regimen involves 4 steps outlined in Table 4.

**Table 4. Conversion From Adjunctive Therapy With Valproate to Monotherapy With LAMICTAL in Patients ≥16 Years of Age With Epilepsy**

| | LAMICTAL | Valproate |
|---|---|---|
| Step 1 | Achieve a dose of 200 mg/day according to guidelines in Table 1 (if not already on 200 mg/day). | Maintain previous stable dose. |
| Step 2 | Maintain at 200 mg/day. | Decrease to 500 mg/day by decrements no greater than 500 mg/day/week and then maintain the dose of 500 mg/day for 1 week. |
| Step 3 | Increase to 300 mg/day and maintain for 1 week. | Simultaneously decrease to 250 mg/day and maintain for 1 week. |
| Step 4 | Increase by 100 mg/day every week to achieve maintenance dose of 500 mg/day. | Discontinue. |

Conversion From Adjunctive Therapy With Antiepileptic Drugs Other Than Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate to Monotherapy With LAMICTAL: No specific dosing guidelines can be provided for conversion to monotherapy with LAMICTAL with AEDs other than carbamazepine, phenobarbital, phenytoin, primidone, or valproate.

### 2.4 Bipolar Disorder

The goal of maintenance treatment with LAMICTAL is to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy. The target dose of LAMICTAL is 200 mg/day (100 mg/day in patients taking valproate, which decreases the apparent clearance of lamotrigine, and 400 mg/day in patients not taking valproate and taking either carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin that increase the apparent clearance of lamotrigine). In the clinical trials, doses up to 400 mg/day as monotherapy were evaluated; however, no additional benefit was seen at 400 mg/day

compared with 200 mg/day *[see Clinical Studies (14.2)]*. Accordingly, doses above 200 mg/day are not recommended. Treatment with LAMICTAL is introduced, based on concurrent medications, according to the regimen outlined in Table 5. If other psychotropic medications are withdrawn following stabilization, the dose of LAMICTAL should be adjusted. For patients discontinuing valproate, the dose of LAMICTAL should be doubled over a 2-week period in equal weekly increments (see Table 6). For patients discontinuing carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin that induce lamotrigine glucuronidation, the dose of LAMICTAL should remain constant for the first week and then should be decreased by half over a 2-week period in equal weekly decrements (see Table 6). The dose of LAMICTAL may then be further adjusted to the target dose (200 mg) as clinically indicated.

If other drugs are subsequently introduced, the dose of LAMICTAL may need to be adjusted. In particular, the introduction of valproate requires reduction in the dose of LAMICTAL *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*.

To avoid an increased risk of rash, the recommended initial dose and subsequent dose escalations of LAMICTAL should not be exceeded *[see Boxed Warning]*.

**Table 5. Escalation Regimen for LAMICTAL for Patients With Bipolar Disorder**

| | For Patients TAKING Valproate[a] | For Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone,[b] or Valproate[a] | For Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone[b] and NOT TAKING Valproate[a] |
|---|---|---|---|
| Weeks 1 and 2 | 25 mg every *other* day | 25 mg daily | 50 mg daily |
| Weeks 3 and 4 | 25 mg daily | 50 mg daily | 100 mg daily, in divided doses |
| Week 5 | 50 mg daily | 100 mg daily | 200 mg daily, in divided doses |
| Week 6 | 100 mg daily | 200 mg daily | 300 mg daily, in divided doses |
| Week 7 | 100 mg daily | 200 mg daily | up to 400 mg daily, in divided doses |

[a]Valproate has been shown to inhibit glucuronidation and decrease the apparent clearance of lamotrigine *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*.

[b]These drugs induce lamotrigine glucuronidation and increase clearance *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*. Other drugs that have similar effects include estrogen-containing oral contraceptives *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*. Dosing recommendations for oral contraceptives can be found in General Dosing Considerations *[see Dosage and Administration (2.1)]*. Patients on rifampin, or other drugs that induce lamotrigine glucuronidation and increase clearance, should follow the same dosing titration/maintenance regimen as that used with anticonvulsants that have this effect.

**Table 6. Dosage Adjustments to LAMICTAL for Patients With Bipolar Disorder Following Discontinuation of Psychotropic Medications**

| | Discontinuation of Psychotropic Drugs (excluding Carbamazepine, Phenytoin, Phenobarbital, Primidone,[b] or Valproate[a]) | After Discontinuation of Valproate[a] | After Discontinuation of Carbamazepine, Phenytoin, |
|---|---|---|---|