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)

----------RECENT MAJOR CHANGES ----------

Warnings and Precautions, Aseptic Meningitis (5.7) Month Year

---------- INDICATIONS AND USAGE ----------

LAMICTAL is an antiepileptic drug (AED) indicated for:

Epilepsy—adjunctive therapy in patients ≥2 years of age: (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)

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)

---------- 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, 5.9)
- LAMICTAL should be discontinued over a period of at least 2 weeks (approximately 50% reduction per week). (2.1, 5.10)

Epilepsy

- 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)

---------- DOSAGE FORMS AND STRENGTHS ----------

Tablets: 25 mg, 100 mg, 150 mg, and 200 mg scored. (3.1, 16)

Chewable Dispersible Tablets: 2 mg, 5 mg, and 25 mg. (3.2, 16)

Orally Disintegrating Tablets: 25 mg, 50 mg, 100 mg, and 200 mg. (3.3, 16)

----------CONTRAINDICATIONS----------

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

---------- WARNINGS AND PRECAUTIONS ----------

- Life-threatening serious rash and/or rash-related death may result. (Boxed Warning, 5.1)
- Hypersensitivity reaction may be fatal or life-threatening. Early signs of hypersensitivity (e.g., fever, lymphadenopathy) may present without rash; if signs present, patient should be evaluated immediately. LAMICTAL should be discontinued if alternate etiology for hypersensitivity signs is not found. (5.2)
- Acute multiorgan failure has resulted (some cases fatal). (5.3)
- Blood dyscrasias (e.g., neutropenia, thrombocytopenia, pancytopenia), may result either with or without an associated hypersensitivity syndrome. (5.4)
- Suicidal behavior and ideation. (5.5)
- 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. (5.6)
- Aseptic meningitis reported in pediatric and adult patients. (5.7)
- 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, 5.8, 16, 17.9)

---------- ADVERSE REACTIONS ----------

- 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.

----------DRUG INTERACTIONS----------

- 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)

---------- USE IN SPECIFIC POPULATIONS ----------

- 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:

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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, in order 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 in order 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 (5.10)]*.

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 (5.10)]*.

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** **100 to 400 mg/day with valproate and other drugs that induce glucuronidation** (in 1 or 2 divided doses)	**225 to 375 mg/day** (in 2 divided doses)	**300 to 500 mg/day** (in 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 which 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 amount to the previously	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 whole tablet, and add this amount to the previously administered daily dose	The dose should be increased every 1 to 2 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

	administered daily dose		
Usual Maintenance Dose	**1 to 5 mg/kg/day** (maximum 200 mg/day in 1 or 2 divided doses). **1 to 3 mg/kg/day** with valproate alone	**4.5 to 7.5 mg/kg/day** (maximum 300 mg/day in 2 divided doses)	**5 to 15 mg/kg/day** (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 which 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 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 AEDs 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 which 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, Phenobarbital, or Primidone[b]
		Current dose of LAMICTAL (mg/day) 100	Current dose of LAMICTAL (mg/day) 400
Week 1	Maintain current dose of LAMICTAL	150	400
Week 2	Maintain current dose of LAMICTAL	200	300
Week 3 onward	Maintain current dose of LAMICTAL	200	200

[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 which 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.

The benefit of continuing treatment in patients who had been stabilized in an 8- to 16-week open-label phase with LAMICTAL was established in 2 randomized, placebo-controlled clinical maintenance trials *[see Clinical Studies (14.2)]*. However, the optimal duration of treatment with LAMICTAL has not been established. Thus, patients should be periodically reassessed to determine the need for maintenance treatment.

2.5 Administration of LAMICTAL Chewable Dispersible Tablets

LAMICTAL Chewable Dispersible Tablets may be swallowed whole, chewed, or dispersed in water or diluted fruit juice. If the tablets are chewed, consume a small amount of water or diluted fruit juice to aid in swallowing.

To disperse LAMICTAL Chewable Dispersible Tablets, add the tablets to a small amount of liquid (1 teaspoon, or enough to cover the medication). Approximately 1 minute later, when the tablets are completely dispersed, swirl the solution and consume the entire quantity immediately. *No attempt should be made to administer partial quantities of the dispersed tablets.*

2.6 Administration of LAMICTAL ODT Orally Disintegrating Tablets

LAMICTAL ODT Orally Disintegrating Tablets should be placed onto the tongue and moved around in the mouth. The tablet will disintegrate rapidly, can be swallowed with or without water, and can be taken with or without food.

3 DOSAGE FORMS AND STRENGTHS

3.1 Tablets

25 mg, white, scored, shield-shaped tablets debossed with “LAMICTAL” and “25”
100 mg, peach, scored, shield-shaped tablets debossed with "LAMICTAL" and "100"
150 mg, cream, scored, shield-shaped tablets debossed with "LAMICTAL" and "150"
200 mg, blue, scored, shield-shaped tablets debossed with "LAMICTAL" and "200"

3.2 Chewable Dispersible Tablets

2 mg, white to off-white, round tablets debossed with “LTG” over “2”
5 mg, white to off-white, caplet-shaped tablets debossed with “GX CL2”
25 mg, white, super elliptical-shaped tablets debossed with “GX CL5”

3.3 Orally Disintegrating Tablets

25 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with “LMT” on one side and “25” on the other side.

50 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with “LMT” on one side and “50” on the other side.

100 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with “LAMICTAL” on one side and “100” on the other side.

200 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with “LAMICTAL” on one side and “200” on the other side.

3.4 Potential Medication Errors

Patients should be strongly advised to visually inspect their tablets to verify that they are receiving LAMICTAL as well as the correct formulation of LAMICTAL each time they fill their prescription. Depictions of the LAMICTAL Tablets, Chewable Dispersible Tablets, and Orally Disintegrating Tablets can be found in the Medication Guide that accompanies the product.

4 CONTRAINDICATIONS

LAMICTAL is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients *[see Boxed Warning, Warnings and Precautions (5.1), (5.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Skin Rashes *[see Boxed Warning]*

Pediatric Population: The incidence of serious rash associated with hospitalization and discontinuation of LAMICTAL in a prospectively followed cohort of pediatric patients (2 to 16 years of age) with epilepsy receiving adjunctive therapy was approximately 0.8% (16 of 1,983). When 14 of these cases were reviewed by 3 expert dermatologists, there was considerable disagreement as to their proper classification. To illustrate, one dermatologist considered none of the cases to be Stevens-Johnson syndrome; another assigned 7 of the 14 to this diagnosis. There was 1 rash-related death in this 1,983-patient cohort. Additionally, there have been rare cases of toxic epidermal necrolysis with and without permanent sequelae and/or death in US and foreign postmarketing experience.

There is evidence that the inclusion of valproate in a multidrug regimen increases the risk of serious, potentially life-threatening rash in pediatric patients. In pediatric patients who used valproate concomitantly, 1.2% (6 of 482) experienced a serious rash compared with 0.6% (6 of 952) patients not taking valproate.

Adult Population: Serious rash associated with hospitalization and discontinuation of LAMICTAL occurred in 0.3% (11 of 3,348) of adult patients who received LAMICTAL in premarketing clinical trials of epilepsy. In the bipolar and other mood disorders clinical trials, the rate of serious rash was 0.08% (1 of 1,233) of adult patients who received LAMICTAL as initial monotherapy and 0.13% (2 of 1,538) of adult patients who received LAMICTAL as adjunctive therapy. No fatalities occurred among these individuals. However, in worldwide postmarketing experience, rare cases of rash-related death have been reported, but their numbers are too few to permit a precise estimate of the rate.

Among the rashes leading to hospitalization were Stevens-Johnson syndrome, toxic epidermal necrolysis, angioedema, and a rash associated with a variable number of the following systemic manifestations: fever, lymphadenopathy, facial swelling, and hematologic and hepatologic abnormalities.

There is evidence that the inclusion of valproate in a multidrug regimen increases the risk of serious, potentially life-threatening rash in adults. Specifically, of 584 patients administered LAMICTAL with valproate in epilepsy clinical trials, 6 (1%) were hospitalized in association

with rash; in contrast, 4 (0.16%) of 2,398 clinical trial patients and volunteers administered LAMICTAL in the absence of valproate were hospitalized.

Patients With History of Allergy or Rash to Other AEDs: 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.

5.2 Hypersensitivity Reactions

Hypersensitivity reactions, some fatal or life-threatening, have also occurred. Some of these reactions have included clinical features of multiorgan failure/dysfunction, including hepatic abnormalities and evidence of disseminated intravascular coagulation. It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even though a rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. LAMICTAL should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Prior to initiation of treatment with LAMICTAL, the patient should be instructed that a rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy) may herald a serious medical event and that the patient should report any such occurrence to a physician immediately.

5.3 Acute Multiorgan Failure

Multiorgan failure, which in some cases has been fatal or irreversible, has been observed in patients receiving LAMICTAL. Fatalities associated with multiorgan failure and various degrees of hepatic failure have been reported in 2 of 3,796 adult patients and 4 of 2,435 pediatric patients who received LAMICTAL in epilepsy clinical trials. No such fatalities have been reported in bipolar patients in clinical trials. Rare fatalities from multiorgan failure have also been reported in compassionate plea and postmarketing use. The majority of these deaths occurred in association with other serious medical events, including status epilepticus and overwhelming sepsis, and hantavirus, making it difficult to identify the initial cause.

Additionally, 3 patients (a 45-year-old woman, a 3.5-year-old boy, and an 11-year-old girl) developed multiorgan dysfunction and disseminated intravascular coagulation 9 to 14 days after LAMICTAL was added to their AED regimens. Rash and elevated transaminases were also present in all patients and rhabdomyolysis was noted in 2 patients. Both pediatric patients were receiving concomitant therapy with valproate, while the adult patient was being treated with carbamazepine and clonazepam. All patients subsequently recovered with supportive care after treatment with LAMICTAL was discontinued.

5.4 Blood Dyscrasias

There have been reports of blood dyscrasias that may or may not be associated with the hypersensitivity syndrome. These have included neutropenia, leukopenia, anemia, thrombocytopenia, pancytopenia, and, rarely, aplastic anemia and pure red cell aplasia.

5.5 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including LAMICTAL, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately 1 case of suicidal thinking or behavior for every 530 patients treated. There were 4 suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number of events is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as 1 week after starting treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanism of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5 to 100 years) in the clinical trials analyzed.

Table 7 shows absolute and relative risk by indication for all evaluated AEDs.

Table 7. Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients With Events Per 1,000 Patients	Drug Patients With Events Per 1,000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients With Events Per 1,000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing LAMICTAL or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

5.6 Use in Patients With Bipolar Disorder

Acute Treatment of Mood Episodes: Safety and effectiveness of LAMICTAL in the acute treatment of mood episodes have not been established.

Children and Adolescents (less than 18 years of age): Safety and effectiveness of LAMICTAL in patients below the age of 18 years with mood disorders have not been established *[see Suicidal Behavior and Ideation (5.5)]*.

Clinical Worsening and Suicide Risk Associated With Bipolar Disorder: Patients with bipolar disorder may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviors (suicidality) whether or not they are taking medications for bipolar disorder. Patients should be closely monitored for clinical worsening (including development of new symptoms) and suicidality, especially at the beginning of a course of treatment or at the time of dose changes.

In addition, patients with a history of suicidal behavior or thoughts, those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults are at an increased risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment *[see Suicidal Behavior and Ideation (5.5)]*.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who experience clinical worsening (including development of new symptoms) and/or the emergence of suicidal ideation/behavior especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Prescriptions for LAMICTAL should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose. Overdoses have been reported for LAMICTAL, some of which have been fatal *[see Overdosage (10.1)]*.

5.7 Aseptic Meningitis

Therapy with LAMICTAL increases the risk of developing aseptic meningitis. Because of the potential for serious outcomes of untreated meningitis due to other causes, patients should also be evaluated for other causes of meningitis and treated as appropriate.

Postmarketing cases of aseptic meningitis have been reported in pediatric and adult patients taking LAMICTAL for various indications. Symptoms upon presentation have included headache, fever, nausea, vomiting, and nuchal rigidity. Rash, photophobia, myalgia, chills, altered consciousness, and somnolence were also noted in some cases. Symptoms have been reported to occur within 1 day to one and a half months following the initiation of treatment. In most cases, symptoms were reported to resolve after discontinuation of LAMICTAL. Re-exposure resulted in a rapid return of symptoms (from within 30 minutes to 1 day following re-initiation of treatment) that were frequently more severe. Some of the patients treated with LAMICTAL who developed aseptic meningitis had underlying diagnoses of systemic lupus erythematosus or other autoimmune diseases.

Cerebrospinal fluid (CSF) analyzed at the time of clinical presentation in reported cases was characterized by a mild to moderate pleocytosis, normal glucose levels, and mild to moderate increase in protein. CSF white blood cell count differentials showed a predominance of neutrophils in a majority of the cases, although a predominance of lymphocytes was reported in approximately one third of the cases. Some patients also had new onset of signs and symptoms of involvement of other organs (predominantly hepatic and renal involvement), which may suggest that in these cases the aseptic meningitis observed was part of a hypersensitivity reaction *[see Warnings and Precautions (5.2)]*.

5.8 Potential Medication Errors

Medication errors involving LAMICTAL have occurred. In particular, the names LAMICTAL or lamotrigine can be confused with the names of other commonly used medications. Medication errors may also occur between the different formulations of LAMICTAL. To reduce the potential of medication errors, write and say LAMICTAL clearly. Depictions of the LAMICTAL Tablets, Chewable Dispersible Tablets, and Orally Disintegrating Tablets can be found in the Medication Guide that accompanies the product to highlight the distinctive markings, colors, and shapes that serve to identify the different presentations of the drug and thus may help reduce the risk of medication errors. To avoid the medication error of using the wrong drug or formulation, patients should be strongly advised to visually inspect their tablets to verify that they are LAMICTAL, as well as the correct formulation of LAMICTAL, each time they fill their prescription.

5.9 Concomitant Use With Oral Contraceptives

Some estrogen-containing oral contraceptives have been shown to decrease serum concentrations of lamotrigine *[see Clinical Pharmacology (12.3)]*. **Dosage adjustments will be necessary in most patients who start or stop estrogen-containing oral contraceptives while taking LAMICTAL** *[see Dosage and Administration (2.1)]*. During the week of inactive hormone preparation (“pill-free” week) of oral contraceptive therapy, plasma lamotrigine levels are expected to rise, as much as doubling at the end of the week. Adverse reactions consistent with elevated levels of lamotrigine, such as dizziness, ataxia, and diplopia, could occur.

5.10 Withdrawal Seizures

As with other AEDs, LAMICTAL should not be abruptly discontinued. In patients with epilepsy there is a possibility of increasing seizure frequency. 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. Unless safety concerns require a more rapid withdrawal, the dose of LAMICTAL should be tapered over a period of at least 2 weeks (approximately 50% reduction per week) *[see Dosage and Administration (2.1)]*.

5.11 Status Epilepticus

Valid estimates of the incidence of treatment-emergent status epilepticus among patients treated with LAMICTAL are difficult to obtain because reporters participating in clinical trials did not all employ identical rules for identifying cases. At a minimum, 7 of 2,343 adult patients had episodes that could unequivocally be described as status epilepticus. In addition, a number of reports of variably defined episodes of seizure exacerbation (e.g., seizure clusters, seizure flurries, etc.) were made.

5.12 Sudden Unexplained Death in Epilepsy (SUDEP)

During the premarketing development of LAMICTAL, 20 sudden and unexplained deaths were recorded among a cohort of 4,700 patients with epilepsy (5,747 patient-years of exposure).

Some of these could represent seizure-related deaths in which the seizure was not observed, e.g., at night. This represents an incidence of 0.0035 deaths per patient-year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving LAMICTAL (ranging from 0.0005 for the general population of patients with epilepsy, to 0.004 for a recently studied clinical trial population similar to that in the clinical development program for LAMICTAL, to 0.005 for patients with refractory epilepsy). Consequently, whether these figures are reassuring or suggest concern depends on the comparability of the populations reported upon to the cohort receiving LAMICTAL and the accuracy of the estimates provided. Probably most reassuring is the similarity of estimated SUDEP rates in patients receiving LAMICTAL and those receiving other AEDs, chemically unrelated to each other, that underwent clinical testing in similar populations. Importantly, that drug is chemically unrelated to LAMICTAL. This evidence suggests, although it certainly does not prove, that the high SUDEP rates reflect population rates, not a drug effect.

5.13 Addition of LAMICTAL to a Multidrug Regimen That Includes Valproate

Because valproate reduces the clearance of lamotrigine, the dosage of lamotrigine in the presence of valproate is less than half of that required in its absence.

5.14 Binding in the Eye and Other Melanin-Containing Tissues

Because lamotrigine binds to melanin, it could accumulate in melanin-rich tissues over time. This raises the possibility that lamotrigine may cause toxicity in these tissues after extended use. Although ophthalmological testing was performed in one controlled clinical trial,

the testing was inadequate to exclude subtle effects or injury occurring after long-term exposure. Moreover, the capacity of available tests to detect potentially adverse consequences, if any, of lamotrigine's binding to melanin is unknown *[see Clinical Pharmacology (12.2)]*.

Accordingly, although there are no specific recommendations for periodic ophthalmological monitoring, prescribers should be aware of the possibility of long-term ophthalmologic effects.

5.15 Laboratory Tests

The value of monitoring plasma concentrations of lamotrigine in patients treated with LAMICTAL has not been established. Because of the possible pharmacokinetic interactions between lamotrigine and other drugs including AEDs (see Table 15), monitoring of the plasma levels of lamotrigine and concomitant drugs may be indicated, particularly during dosage adjustments. In general, clinical judgment should be exercised regarding monitoring of plasma levels of lamotrigine and other drugs and whether or not dosage adjustments are necessary.

6 ADVERSE REACTIONS

The following adverse reactions are described in more detail in the *Warnings and Precautions* section of the label:

- Serious skin rashes *[see Warnings and Precautions (5.1)]*
- Hypersensitivity reactions *[see Warnings and Precautions (5.2)]*
- Acute multiorgan failure *[see Warnings and Precautions (5.3)]*
- Blood dyscrasias *[see Warnings and Precautions (5.4)]*
- Suicidal behavior and ideation *[see Warnings and Precautions (5.5)]*
- Aseptic meningitis *[see Warnings and Precautions (5.7)]*
- Withdrawal seizures *[see Warnings and Precautions (5.10)]*
- Status epilepticus *[see Warnings and Precautions (5.11)]*
- Sudden unexplained death in epilepsy *[see Warnings and Precautions (5.12)]*

6.1 Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

LAMICTAL has been evaluated for safety in patients with epilepsy and in patients with Bipolar I Disorder. Adverse reactions reported for each of these patient populations are provided below. Excluded are adverse reactions considered too general to be informative and those not reasonably attributable to the use of the drug.

Epilepsy: *Most Common Adverse Reactions in All Clinical Studies: Adjunctive Therapy in Adults With Epilepsy:* The most commonly observed (≥5% for LAMICTAL and more common on drug than placebo) adverse reactions seen in association with LAMICTAL during adjunctive therapy in adults and not seen at an equivalent frequency among placebo-treated patients were: dizziness, ataxia, somnolence, headache, diplopia, blurred vision, nausea, vomiting, and rash. Dizziness, diplopia, ataxia, blurred vision, nausea, and vomiting were dose-

related. Dizziness, diplopia, ataxia, and blurred vision occurred more commonly in patients receiving carbamazepine with LAMICTAL than in patients receiving other AEDs with LAMICTAL. Clinical data suggest a higher incidence of rash, including serious rash, in patients receiving concomitant valproate than in patients not receiving valproate *[see Warnings and Precautions (5.1)]*.

Approximately 11% of the 3,378 adult patients who received LAMICTAL as adjunctive therapy in premarketing clinical trials discontinued treatment because of an adverse reaction. The adverse reactions most commonly associated with discontinuation were rash (3.0%), dizziness (2.8%), and headache (2.5%).

In a dose-response study in adults, the rate of discontinuation of LAMICTAL for dizziness, ataxia, diplopia, blurred vision, nausea, and vomiting was dose-related.

Monotherapy in Adults With Epilepsy: The most commonly observed (≥5% for LAMICTAL and more common on drug than placebo) adverse reactions seen in association with the use of LAMICTAL during the monotherapy phase of the controlled trial in adults not seen at an equivalent rate in the control group were vomiting, coordination abnormality, dyspepsia, nausea, dizziness, rhinitis, anxiety, insomnia, infection, pain, weight decrease, chest pain, and dysmenorrhea. The most commonly observed (≥5% for LAMICTAL and more common on drug than placebo) adverse reactions associated with the use of LAMICTAL during the conversion to monotherapy (add-on) period, not seen at an equivalent frequency among low-dose valproate-treated patients, were dizziness, headache, nausea, asthenia, coordination abnormality, vomiting, rash, somnolence, diplopia, ataxia, accidental injury, tremor, blurred vision, insomnia, nystagmus, diarrhea, lymphadenopathy, pruritus, and sinusitis.

Approximately 10% of the 420 adult patients who received LAMICTAL as monotherapy in premarketing clinical trials discontinued treatment because of an adverse reaction. The adverse reactions most commonly associated with discontinuation were rash (4.5%), headache (3.1%), and asthenia (2.4%).

Adjunctive Therapy in Pediatric Patients With Epilepsy: The most commonly observed (≥5% for LAMICTAL and more common on drug than placebo) adverse reactions seen in association with the use of LAMICTAL as adjunctive treatment in pediatric patients 2 to 16 years of age and not seen at an equivalent rate in the control group were infection, vomiting, rash, fever, somnolence, accidental injury, dizziness, diarrhea, abdominal pain, nausea, ataxia, tremor, asthenia, bronchitis, flu syndrome, and diplopia.

In 339 patients 2 to 16 years of age with partial seizures or generalized seizures of Lennox-Gastaut syndrome, 4.2% of patients on LAMICTAL and 2.9% of patients on placebo discontinued due to adverse reactions. The most commonly reported adverse reaction that led to discontinuation of LAMICTAL was rash.

Approximately 11.5% of the 1,081 pediatric patients 2 to 16 years of age who received LAMICTAL as adjunctive therapy in premarketing clinical trials discontinued treatment because

of an adverse reaction. The adverse reactions most commonly associated with discontinuation were rash (4.4%), reaction aggravated (1.7%), and ataxia (0.6%).

Controlled Adjunctive Clinical Studies in Adults With Epilepsy: Table 8 lists treatment-emergent adverse reactions that occurred in at least 2% of adult patients with epilepsy treated with LAMICTAL in placebo-controlled trials and were numerically more common in the patients treated with LAMICTAL. In these studies, either LAMICTAL or placebo was added to the patient's current AED therapy. Adverse reactions were usually mild to moderate in intensity.

Table 8. Treatment-Emergent Adverse Reaction Incidence in Placebo-Controlled Adjunctive Trials in Adult Patients With Epilepsy[a] (Adverse reactions in at least 2% of patients treated with LAMICTAL and numerically more frequent than in the placebo group.)

Body System/ Adverse Reaction	Percent of Patients Receiving Adjunctive LAMICTAL (n = 711)	Percent of Patients Receiving Adjunctive Placebo (n = 419)
Body as a whole		
Headache	29	19
Flu syndrome	7	6
Fever	6	4
Abdominal pain	5	4
Neck pain	2	1
Reaction aggravated (seizure exacerbation)	2	1
Digestive		
Nausea	19	10
Vomiting	9	4
Diarrhea	6	4
Dyspepsia	5	2
Constipation	4	3
Anorexia	2	1
Musculoskeletal		
Arthralgia	2	0
Nervous		
Dizziness	38	13
Ataxia	22	6
Somnolence	14	7
Incoordination	6	2
Insomnia	6	2

Tremor	4	1
Depression	4	3
Anxiety	4	3
Convulsion	3	1
Irritability	3	2
Speech disorder	3	0
Concentration disturbance	2	1
Respiratory		
Rhinitis	14	9
Pharyngitis	10	9
Cough increased	8	6
Skin and appendages		
Rash	10	5
Pruritus	3	2
Special senses		
Diplopia	28	7
Blurred vision	16	5
Vision abnormality	3	1
Urogenital		
Female patients only	(n = 365)	(n = 207)
Dysmenorrhea	7	6
Vaginitis	4	1
Amenorrhea	2	1

[a] Patients in these adjunctive studies were receiving 1 to 3 of the following concomitant AEDs (carbamazepine, phenytoin, phenobarbital, or primidone) in addition to LAMICTAL or placebo. Patients may have reported multiple adverse reactions during the study or at discontinuation; thus, patients may be included in more than one category.

In a randomized, parallel study comparing placebo and 300 and 500 mg/day of LAMICTAL, some of the more common drug-related adverse reactions were dose-related (see Table 9).

Table 9. Dose-Related Adverse Reactions From a Randomized, Placebo-Controlled Adjunctive Trial in Adults With Epilepsy

	Percent of Patients Experiencing Adverse Reactions		
Adverse Reaction	Placebo (n = 73)	LAMICTAL 300 mg (n = 71)	LAMICTAL 500 mg (n = 72)
Ataxia	10	10	28[ab]
Blurred vision	10	11	25[ab]
Diplopia	8	24[a]	49[ab]
Dizziness	27	31	54[ab]
Nausea	11	18	25[a]
Vomiting	4	11	18[a]

[a] Significantly greater than placebo group ($p<0.05$).

[b] Significantly greater than group receiving LAMICTAL 300 mg ($p<0.05$).

The overall adverse reaction profile for LAMICTAL was similar between females and males, and was independent of age. Because the largest non-Caucasian racial subgroup was only 6% of patients exposed to LAMICTAL in placebo-controlled trials, there are insufficient data to support a statement regarding the distribution of adverse reaction reports by race. Generally, females receiving either LAMICTAL as adjunctive therapy or placebo were more likely to report adverse reactions than males. The only adverse reaction for which the reports on LAMICTAL were greater than 10% more frequent in females than males (without a corresponding difference by gender on placebo) was dizziness (difference = 16.5%). There was little difference between females and males in the rates of discontinuation of LAMICTAL for individual adverse reactions.

Controlled Monotherapy Trial in Adults With Partial Seizures: Table 10 lists treatment-emergent adverse reactions that occurred in at least 5% of patients with epilepsy treated with monotherapy with LAMICTAL in a double-blind trial following discontinuation of either concomitant carbamazepine or phenytoin not seen at an equivalent frequency in the control group.

Table 10. Treatment-Emergent Adverse Reaction Incidence in Adults With Partial Seizures in a Controlled Monotherapy Trial[a] (Adverse reactions in at least 5% of patients treated with LAMICTAL and numerically more frequent than in the valproate group.)

Body System/ Adverse Reaction	Percent of Patients Receiving LAMICTAL as Monotherapy[b] (n = 43)	Percent of Patients Receiving Low-Dose Valproate[c] Monotherapy (n = 44)
Body as a whole		

Pain	5	0
Infection	5	2
Chest pain	5	2
Digestive		
Vomiting	9	0
Dyspepsia	7	2
Nausea	7	2
Metabolic and nutritional		
Weight decrease	5	2
Nervous		
Coordination abnormality	7	0
Dizziness	7	0
Anxiety	5	0
Insomnia	5	2
Respiratory		
Rhinitis	7	2
Urogenital (female patients only)	(n = 21)	(n = 28)
Dysmenorrhea	5	0

[a] Patients in these studies were converted to LAMICTAL or valproate monotherapy from adjunctive therapy with carbamazepine or phenytoin. Patients may have reported multiple adverse reactions during the study; thus, patients may be included in more than one category.
[b] Up to 500 mg/day.
[c] 1,000 mg/day.

Adverse reactions that occurred with a frequency of less than 5% and greater than 2% of patients receiving LAMICTAL and numerically more frequent than placebo were:

Body as a Whole: Asthenia, fever.

Digestive: Anorexia, dry mouth, rectal hemorrhage, peptic ulcer.

Metabolic and Nutritional: Peripheral edema.

Nervous System: Amnesia, ataxia, depression, hypesthesia, libido increase, decreased reflexes, increased reflexes, nystagmus, irritability, suicidal ideation.

Respiratory: Epistaxis, bronchitis, dyspnea.

Skin and Appendages: Contact dermatitis, dry skin, sweating.

Special Senses: Vision abnormality.

Incidence in Controlled Adjunctive Trials in Pediatric Patients With Epilepsy: Table 11 lists adverse reactions that occurred in at least 2% of 339 pediatric patients with partial seizures or generalized seizures of Lennox-Gastaut syndrome, who received

LAMICTAL up to 15 mg/kg/day or a maximum of 750 mg/day. Reported adverse reactions were classified using COSTART terminology.

Table 11. Treatment-Emergent Adverse Reaction Incidence in Placebo-Controlled Adjunctive Trials in Pediatric Patients With Epilepsy (Adverse reactions in at least 2% of patients treated with LAMICTAL and numerically more frequent than in the placebo group.)

Body System/ Adverse Reaction	Percent of Patients Receiving LAMICTAL (n = 168)	Percent of Patients Receiving Placebo (n = 171)
Body as a whole		
Infection	20	17
Fever	15	14
Accidental injury	14	12
Abdominal pain	10	5
Asthenia	8	4
Flu syndrome	7	6
Pain	5	4
Facial edema	2	1
Photosensitivity	2	0
Cardiovascular		
Hemorrhage	2	1
Digestive		
Vomiting	20	16
Diarrhea	11	9
Nausea	10	2
Constipation	4	2
Dyspepsia	2	1
Hemic and lymphatic		
Lymphadenopathy	2	1
Metabolic and nutritional		
Edema	2	0
Nervous system		
Somnolence	17	15
Dizziness	14	4
Ataxia	11	3
Tremor	10	1
Emotional lability	4	2
Gait abnormality	4	2

Thinking abnormality	3	2
Convulsions	2	1
Nervousness	2	1
Vertigo	2	1
Respiratory		
Pharyngitis	14	11
Bronchitis	7	5
Increased cough	7	6
Sinusitis	2	1
Bronchospasm	2	1
Skin		
Rash	14	12
Eczema	2	1
Pruritus	2	1
Special senses		
Diplopia	5	1
Blurred vision	4	1
Visual abnormality	2	0
Urogenital		
Male and female patients		
Urinary tract infection	3	0

Bipolar Disorder: The most commonly observed (≥5%) treatment-emergent adverse reactions seen in association with the use of LAMICTAL as monotherapy (100 to 400 mg/day) in adult patients (≥18 years of age) with Bipolar Disorder in the 2 double-blind, placebo-controlled trials of 18 months' duration, and numerically more frequent than in placebo-treated patients are included in Table 12. Adverse reactions that occurred in at least 5% of patients and were numerically more common during the dose-escalation phase of LAMICTAL in these trials (when patients may have been receiving concomitant medications) compared with the monotherapy phase were: headache (25%), rash (11%), dizziness (10%), diarrhea (8%), dream abnormality (6%), and pruritus (6%).

During the monotherapy phase of the double-blind, placebo-controlled trials of 18 months' duration, 13% of 227 patients who received LAMICTAL (100 to 400 mg/day), 16% of 190 patients who received placebo, and 23% of 166 patients who received lithium discontinued therapy because of an adverse reaction. The adverse reactions which most commonly led to discontinuation of LAMICTAL were rash (3%) and mania/hypomania/mixed mood adverse reactions (2%). Approximately 16% of 2,401 patients who received LAMICTAL (50 to 500 mg/day) for Bipolar Disorder in premarketing trials discontinued therapy because of

an adverse reaction; most commonly due to rash (5%) and mania/hypomania/mixed mood adverse reactions (2%).

The overall adverse reaction profile for LAMICTAL was similar between females and males, between elderly and nonelderly patients, and among racial groups.

Table 12. Treatment-Emergent Adverse Reaction Incidence in 2 Placebo-Controlled Trials in Adults With Bipolar I Disorder[a] (Adverse reactions in at least 5% of patients treated with LAMICTAL as monotherapy and numerically more frequent than in the placebo group.)

Body System/ Adverse Reaction	Percent of Patients Receiving LAMICTAL (n = 227)	Percent of Patients Receiving Placebo (n = 190)
General		
Back pain	8	6
Fatigue	8	5
Abdominal pain	6	3
Digestive		
Nausea	14	11
Constipation	5	2
Vomiting	5	2
Nervous System		
Insomnia	10	6
Somnolence	9	7
Xerostomia (dry mouth)	6	4
Respiratory		
Rhinitis	7	4
Exacerbation of cough	5	3
Pharyngitis	5	4
Skin		
Rash (nonserious)[b]	7	5

[a] Patients in these studies were converted to LAMICTAL (100 to 400 mg/day) or placebo monotherapy from add-on therapy with other psychotropic medications. Patients may have reported multiple adverse reactions during the study; thus, patients may be included in more than one category.

[b] In the overall bipolar and other mood disorders clinical trials, the rate of serious rash was 0.08% (1 of 1,233) of adult patients who received LAMICTAL as initial monotherapy and 0.13% (2 of 1,538) of adult patients who received LAMICTAL as adjunctive therapy *[see Warnings and Precautions (5.1)]*.

These adverse reactions were usually mild to moderate in intensity. Other reactions that occurred in 5% or more patients but equally or more frequently in the placebo group included: dizziness, mania, headache, infection, influenza, pain, accidental injury, diarrhea, and dyspepsia.

Adverse reactions that occurred with a frequency of less than 5% and greater than 1% of patients receiving LAMICTAL and numerically more frequent than placebo were:

General: Fever, neck pain.

Cardiovascular: Migraine.

Digestive: Flatulence

Metabolic and Nutritional: Weight gain, edema.

Musculoskeletal: Arthralgia, myalgia.

Nervous System: Amnesia, depression, agitation, emotional lability, dyspraxia, abnormal thoughts, dream abnormality, hypoesthesia.

Respiratory: Sinusitis.

Urogenital: Urinary frequency.

Adverse Reactions Following Abrupt Discontinuation: In the 2 maintenance trials, there was no increase in the incidence, severity or type of adverse reactions in Bipolar Disorder patients after abruptly terminating therapy with 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 *[see Warnings and Precautions (5.10)]*.

Mania/Hypomania/Mixed Episodes: During the double-blind, placebo-controlled clinical trials in Bipolar I Disorder in which patients were converted to monotherapy with LAMICTAL (100 to 400 mg/day) from other psychotropic medications and followed for up to 18 months, the rates of manic or hypomanic or mixed mood episodes reported as adverse reactions were 5% for patients treated with LAMICTAL (n = 227), 4% for patients treated with lithium (n = 166), and 7% for patients treated with placebo (n = 190). In all bipolar controlled trials combined, adverse reactions of mania (including hypomania and mixed mood episodes) were reported in 5% of patients treated with LAMICTAL (n = 956), 3% of patients treated with lithium (n = 280), and 4% of patients treated with placebo (n = 803).

6.2 Other Adverse Reactions Observed in All Clinical Trials

LAMICTAL has been administered to 6,694 individuals for whom complete adverse reaction data was captured during all clinical trials, only some of which were placebo controlled. During these trials, all adverse reactions were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse reactions, similar types of adverse reactions were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. The frequencies presented represent the proportion of the 6,694 individuals exposed to LAMICTAL who experienced an event of the type cited on at least one occasion while receiving LAMICTAL. All reported adverse reactions are included except those already listed in the

previous tables or elsewhere in the labeling, those too general to be informative, and those not reasonably associated with the use of the drug.

Adverse reactions are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* adverse reactions are defined as those occurring in at least 1/100 patients; *infrequent* adverse reactions are those occurring in 1/100 to 1/1,000 patients; *rare* adverse reactions are those occurring in fewer than 1/1,000 patients.

Body as a Whole: *Infrequent:* Allergic reaction, chills, and malaise.

Cardiovascular System: *Infrequent:* Flushing, hot flashes, hypertension, palpitations, postural hypotension, syncope, tachycardia, and vasodilation.

Dermatological: *Infrequent:* Acne, alopecia, hirsutism, maculopapular rash, skin discoloration, and urticaria. *Rare:* Angioedema, erythema, exfoliative dermatitis, fungal dermatitis, herpes zoster, leukoderma, multiforme erythema, petechial rash, pustular rash, Stevens-Johnson syndrome, and vesiculobullous rash.

Digestive System: *Infrequent:* Dysphagia, eructation, gastritis, gingivitis, increased appetite, increased salivation, liver function tests abnormal, and mouth ulceration. *Rare:* Gastrointestinal hemorrhage, glossitis, gum hemorrhage, gum hyperplasia, hematemesis, hemorrhagic colitis, hepatitis, melena, stomach ulcer, stomatitis, and tongue edema.

Endocrine System: *Rare:* Goiter and hypothyroidism.

Hematologic and Lymphatic System: *Infrequent:* Ecchymosis and leukopenia. *Rare:* Anemia, eosinophilia, fibrin decrease, fibrinogen decrease, iron deficiency anemia, leukocytosis, lymphocytosis, macrocytic anemia, petechia, and thrombocytopenia.

Metabolic and Nutritional Disorders: *Infrequent:* Aspartate transaminase increased. *Rare:* Alcohol intolerance, alkaline phosphatase increase, alanine transaminase increase, bilirubinemia, general edema, gamma glutamyl transpeptidase increase, and hyperglycemia.

Musculoskeletal System: *Infrequent:* Arthritis, leg cramps, myasthenia, and twitching. *Rare:* Bursitis, muscle atrophy, pathological fracture, and tendinous contracture.

Nervous System: *Frequent:* Confusion and paresthesia. *Infrequent:* Akathisia, apathy, aphasia, CNS depression, depersonalization, dysarthria, dyskinesia, euphoria, hallucinations, hostility, hyperkinesia, hypertonia, libido decreased, memory decrease, mind racing, movement disorder, myoclonus, panic attack, paranoid reaction, personality disorder, psychosis, sleep disorder, stupor, and suicidal ideation. *Rare:* Choreoathetosis, delirium, delusions, dysphoria, dystonia, extrapyramidal syndrome, faintness, grand mal convulsions, hemiplegia, hyperalgesia, hyperesthesia, hypokinesia, hypotonia, manic depression reaction, muscle spasm, neuralgia, neurosis, paralysis, and peripheral neuritis.

Respiratory System: *Infrequent:* Yawn. *Rare:* Hiccup and hyperventilation.

Special Senses: *Frequent:* Amblyopia. *Infrequent:* Abnormality of accommodation, conjunctivitis, dry eyes, ear pain, photophobia, taste perversion, and tinnitus. *Rare:* Deafness,

lacrimation disorder, oscillopsia, parosmia, ptosis, strabismus, taste loss, uveitis, and visual field defect.

Urogenital System: *Infrequent:* Abnormal ejaculation, hematuria, impotence, menorrhagia, polyuria, and urinary incontinence. *Rare:* Acute kidney failure, anorgasmia, breast abscess, breast neoplasm, creatinine increase, cystitis, dysuria, epididymitis, female lactation, kidney failure, kidney pain, nocturia, urinary retention, and urinary urgency.

6.3 Postmarketing Experience

The following adverse events (not listed above in clinical trials or other sections of the prescribing information) have been identified during postapproval use of LAMICTAL. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic: Agranulocytosis, hemolytic anemia

Gastrointestinal: Esophagitis.

Hepatobiliary Tract and Pancreas: Pancreatitis.

Immunologic: Lupus-like reaction, vasculitis.

Lower Respiratory: Apnea.

Musculoskeletal: Rhabdomyolysis has been observed in patients experiencing hypersensitivity reactions.

Neurology: Exacerbation of Parkinsonian symptoms in patients with pre-existing Parkinson's disease, tics.

Non-site Specific: Progressive immunosuppression.

7 DRUG INTERACTIONS

Significant drug interactions with lamotrigine are summarized in Table 13. Additional details of these drug interaction studies are provided in the Clinical Pharmacology section *[see Clinical Pharmacology (12.3)]*.

Table 13. Established and Other Potentially Significant Drug Interactions

Concomitant Drug	Effect on Concentration of Lamotrigine or Concomitant Drug	Clinical Comment
Estrogen-containing oral contraceptive preparations containing 30 mcg ethinylestradiol and 150 mcg levonorgestrel	↓ lamotrigine	Decreased lamotrigine levels approximately 50%.
	↓ levonorgestrel	Decrease in levonorgestrel component by 19%.

Carbamazepine (CBZ) and CBZ epoxide	↓ lamotrigine ? CBZ epoxide	Addition of carbamazepine decreases lamotrigine concentration approximately 40%. May increase CBZ epoxide levels
Phenobarbital/Primidone	↓ lamotrigine	Decreased lamotrigine concentration approximately 40%.
Phenytoin (PHT)	↓ lamotrigine	Decreased lamotrigine concentration approximately 40%.
Rifampin	↓ lamotrigine	Decreased lamotrigine AUC approximately 40%.
Valproate	↑ lamotrigine ? valproate	Increased lamotrigine concentrations slightly more than 2-fold. Decreased valproate concentrations an average of 25% over a 3-week period then stabilized in healthy volunteers; no change in controlled clinical trials in epilepsy patients.

↓ = Decreased (induces lamotrigine glucuronidation).
↑ = Increased (inhibits lamotrigine glucuronidation).
? = Conflicting data.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C. No evidence of teratogenicity was found in mice, rats, or rabbits when lamotrigine was orally administered to pregnant animals during the period of organogenesis at doses up to 1.2, 0.5, and 1.1 times, respectively, on a mg/m^2 basis, the highest usual human maintenance dose (i.e., 500 mg/day). However, maternal toxicity and secondary fetal toxicity producing reduced fetal weight and/or delayed ossification were seen in mice and rats, but not in rabbits at these doses. Teratology studies were also conducted using bolus intravenous administration of the isethionate salt of lamotrigine in rats and rabbits. In rat dams administered an intravenous dose at 0.6 times the highest usual human maintenance dose, the incidence of intrauterine death without signs of teratogenicity was increased.

A behavioral teratology study was conducted in rats dosed during the period of organogenesis. At day 21 postpartum, offspring of dams receiving 5 mg/kg/day or higher displayed a significantly longer latent period for open field exploration and a lower frequency of rearing. In a swimming maze test performed on days 39 to 44 postpartum, time to completion

was increased in offspring of dams receiving 25 mg/kg/day. These doses represent 0.1 and 0.5 times the clinical dose on a mg/m^2 basis, respectively.

Lamotrigine did not affect fertility, teratogenesis, or postnatal development when rats were dosed prior to and during mating, and throughout gestation and lactation at doses equivalent to 0.4 times the highest usual human maintenance dose on a mg/m^2 basis.

When pregnant rats were orally dosed at 0.1, 0.14, or 0.3 times the highest human maintenance dose (on a mg/m^2 basis) during the latter part of gestation (days 15 to 20), maternal toxicity and fetal death were seen. In dams, food consumption and weight gain were reduced, and the gestation period was slightly prolonged (22.6 vs. 22.0 days in the control group). Stillborn pups were found in all 3 drug-treated groups with the highest number in the high-dose group. Postnatal death was also seen, but only in the 2 highest doses, and occurred between days 1 and 20. Some of these deaths appear to be drug-related and not secondary to the maternal toxicity. A no-observed-effect level (NOEL) could not be determined for this study.

Although lamotrigine was not found to be teratogenic in the above studies, lamotrigine decreases fetal folate concentrations in rats, an effect known to be associated with teratogenesis in animals and humans. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-Teratogenic Effects: As with other AEDs, physiological changes during pregnancy may affect lamotrigine concentrations and/or therapeutic effect. There have been reports of decreased lamotrigine concentrations during pregnancy and restoration of pre-partum concentrations after delivery. Dosage adjustments may be necessary to maintain clinical response.

Pregnancy Exposure Registry: To provide information regarding the effects of in utero exposure to LAMICTAL, physicians are advised to recommend that pregnant patients taking LAMICTAL enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll-free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

Physicians are also encouraged to register patients in the Lamotrigine Pregnancy Registry; enrollment in this registry must be done prior to any prenatal diagnostic tests and **before fetal outcome is known. Physicians** can obtain information by calling the Lamotrigine Pregnancy Registry at 1-800-336-2176 (toll-free).

8.2 Labor and Delivery

The effect of LAMICTAL on labor and delivery in humans is unknown.

8.3 Nursing Mothers

Preliminary data indicate that lamotrigine passes into human milk. Because the effects on the infant exposed to lamotrigine by this route are unknown, breastfeeding while taking LAMICTAL is not recommended.

8.4 Pediatric Use

LAMICTAL is indicated for adjunctive therapy in patients ≥2 years of age for partial seizures, the generalized seizures of Lennox-Gastaut syndrome, and primary generalized tonic-clonic seizures.

Safety and efficacy of LAMICTAL, used as adjunctive treatment for partial seizures, were not demonstrated in a small randomized, double-blind, placebo-controlled, withdrawal study in very young pediatric patients (1 to 24 months). LAMICTAL was associated with an increased risk for infectious adverse reactions (LAMICTAL 37%, Placebo 5%), and respiratory adverse reactions (LAMICTAL 26%, Placebo 5%). Infectious adverse reactions included bronchiolitis, bronchitis, ear infection, eye infection, otitis externa, pharyngitis, urinary tract infection, and viral infection. Respiratory adverse reactions included nasal congestion, cough, and apnea.

Safety and effectiveness in patients below the age of 18 years with Bipolar Disorder have not been established.

8.5 Geriatric Use

Clinical studies of LAMICTAL for epilepsy and in Bipolar Disorder did not include sufficient numbers of subjects 65 years of age and over to determine whether they respond differently from younger subjects or exhibit a different safety profile than that of younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 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 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 *[see Dosage and Administration (2.1)]*.

8.7 Patients With Renal Impairment

Lamotrigine is metabolized mainly by glucuronic acid conjugation, with the majority of the metabolites being recovered in the urine. In a small study comparing a single dose of lamotrigine in patients with varying degrees of renal impairment with healthy volunteers, the plasma half-life of lamotrigine was significantly longer in the patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

Initial doses of LAMICTAL should be based on patients' AED regimens; reduced maintenance doses may be effective for patients with significant renal impairment. 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 *[see Dosage and Administration (2.1)]*.

10 OVERDOSAGE

10.1 Human Overdose Experience

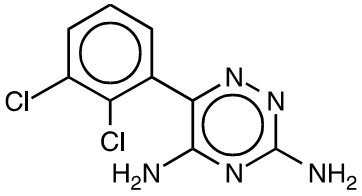
Overdoses involving quantities up to 15 g have been reported for LAMICTAL, some of which have been fatal. Overdose has resulted in ataxia, nystagmus, increased seizures, decreased level of consciousness, coma, and intraventricular conduction delay.

10.2 Management of Overdose

There are no specific antidotes for lamotrigine. Following a suspected overdose, hospitalization of the patient is advised. General supportive care is indicated, including frequent monitoring of vital signs and close observation of the patient. If indicated, emesis should be induced; usual precautions should be taken to protect the airway. It should be kept in mind that lamotrigine is rapidly absorbed *[see Clinical Pharmacology (12.3)]*. It is uncertain whether hemodialysis is an effective means of removing lamotrigine from the blood. In 6 renal failure patients, about 20% of the amount of lamotrigine in the body was removed by hemodialysis during a 4-hour session. A Poison Control Center should be contacted for information on the management of overdosage of LAMICTAL.

11 DESCRIPTION

LAMICTAL (lamotrigine), an AED of the phenyltriazine class, is chemically unrelated to existing AEDs. Its chemical name is 3,5-diamino-6-(2,3-dichlorophenyl)-*as*-triazine, its molecular formula is $C_9H_7N_5Cl_2$, and its molecular weight is 256.09. Lamotrigine is a white to pale cream-colored powder and has a pK_a of 5.7. Lamotrigine is very slightly soluble in water (0.17 mg/mL at 25°C) and slightly soluble in 0.1 M HCl (4.1 mg/mL at 25°C). The structural formula is:



LAMICTAL Tablets are supplied for oral administration as 25 mg (white), 100 mg (peach), 150 mg (cream), and 200 mg (blue) tablets. Each tablet contains the labeled amount of lamotrigine and the following inactive ingredients: lactose; magnesium stearate; microcrystalline cellulose; povidone; sodium starch glycolate; FD&C Yellow No. 6 Lake (100 mg tablet only); ferric oxide, yellow (150 mg tablet only); and FD&C Blue No. 2 Lake (200 mg tablet only).

LAMICTAL Chewable Dispersible Tablets are supplied for oral administration. The tablets contain 2 mg (white), 5 mg (white), or 25 mg (white) of lamotrigine and the following inactive ingredients: blackcurrant flavor, calcium carbonate, low-substituted hydroxypropylcellulose, magnesium aluminum silicate, magnesium stearate, povidone, saccharin sodium, and sodium starch glycolate.

LAMICTAL ODT Orally Disintegrating Tablets are supplied for oral administration. The tablets contain 25 mg (white to off-white), 50 mg (white to off-white), 100 mg (white to off-white), or 200 mg (white to off-white) of lamotrigine and the following inactive ingredients: artificial cherry flavor, crospovidone, ethylcellulose, magnesium stearate, mannitol, polyethylene, and sucralose.

LAMICTAL ODT Orally Disintegrating Tablets are formulated using technologies (Microcaps® and AdvaTab®) designed to mask the bitter taste of lamotrigine and achieve a rapid dissolution profile. Tablet characteristics including flavor, mouth-feel, after-taste, and ease of use were rated as favorable in a study of 108 healthy volunteers.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism(s) by which lamotrigine exerts its anticonvulsant action are unknown. In animal models designed to detect anticonvulsant activity, lamotrigine was effective in preventing seizure spread in the maximum electroshock (MES) and pentylenetetrazol (scMet) tests, and prevented seizures in the visually and electrically evoked after-discharge (EEAD) tests for antiepileptic activity. Lamotrigine also displayed inhibitory properties in the kindling model in rats both during kindling development and in the fully kindled state. The relevance of these models to human epilepsy, however, is not known.

One proposed mechanism of action of lamotrigine, the relevance of which remains to be established in humans, involves an effect on sodium channels. In vitro pharmacological studies suggest that lamotrigine inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal membranes and consequently modulating presynaptic transmitter release of excitatory amino acids (e.g., glutamate and aspartate).

Although the relevance for human use is unknown, the following data characterize the performance of lamotrigine in receptor binding assays. Lamotrigine had a weak inhibitory effect on the serotonin 5-HT_3 receptor (IC_{50} = 18 µM). It does not exhibit high affinity binding (IC_{50}>100 µM) to the following neurotransmitter receptors: adenosine A_1 and A_2; adrenergic α_1, α_2, and β; dopamine D_1 and D_2; γ-aminobutyric acid (GABA) A and B; histamine H_1; kappa opioid; muscarinic acetylcholine; and serotonin 5-HT_2. Studies have failed to detect an effect of lamotrigine on dihydropyridine-sensitive calcium channels. It had weak effects at sigma opioid receptors (IC_{50} = 145 µM). Lamotrigine did not inhibit the uptake of norepinephrine, dopamine, or serotonin (IC_{50}>200 µM) when tested in rat synaptosomes and/or human platelets in vitro.

Effect of Lamotrigine on N-Methyl d-Aspartate-Receptor Mediated Activity:
Lamotrigine did not inhibit N-methyl d-aspartate (NMDA)-induced depolarizations in rat cortical

slices or NMDA-induced cyclic GMP formation in immature rat cerebellum, nor did lamotrigine displace compounds that are either competitive or noncompetitive ligands at this glutamate receptor complex (CNQX, CGS, TCHP). The IC_{50} for lamotrigine effects on NMDA-induced currents (in the presence of 3 µM of glycine) in cultured hippocampal neurons exceeded 100 µM.

The mechanisms by which lamotrigine exerts its therapeutic action in Bipolar Disorder have not been established.

12.2 Pharmacodynamics

Folate Metabolism: In vitro, lamotrigine inhibited dihydrofolate reductase, the enzyme that catalyzes the reduction of dihydrofolate to tetrahydrofolate. Inhibition of this enzyme may interfere with the biosynthesis of nucleic acids and proteins. When oral daily doses of lamotrigine were given to pregnant rats during organogenesis, fetal, placental, and maternal folate concentrations were reduced. Significantly reduced concentrations of folate are associated with teratogenesis *[see Use in Specific Populations (8.1)]*. Folate concentrations were also reduced in male rats given repeated oral doses of lamotrigine. Reduced concentrations were partially returned to normal when supplemented with folinic acid.

Accumulation in Kidneys: Lamotrigine accumulated in the kidney of the male rat, causing chronic progressive nephrosis, necrosis, and mineralization. These findings are attributed to α-2 microglobulin, a species- and sex-specific protein that has not been detected in humans or other animal species.

Melanin Binding: Lamotrigine binds to melanin-containing tissues, e.g., in the eye and pigmented skin. It has been found in the uveal tract up to 52 weeks after a single dose in rodents.

Cardiovascular: In dogs, lamotrigine is extensively metabolized to a 2-N-methyl metabolite. This metabolite causes dose-dependent prolongations of the PR interval, widening of the QRS complex, and, at higher doses, complete AV conduction block. Similar cardiovascular effects are not anticipated in humans because only trace amounts of the 2-N-methyl metabolite (<0.6% of lamotrigine dose) have been found in human urine *[see Clinical Pharmacology (12.3)]*. However, it is conceivable that plasma concentrations of this metabolite could be increased in patients with a reduced capacity to glucuronidate lamotrigine (e.g., in patients with liver disease).

12.3 Pharmacokinetics

The pharmacokinetics of lamotrigine have been studied in patients with epilepsy, healthy young and elderly volunteers, and volunteers with chronic renal failure. Lamotrigine pharmacokinetic parameters for adult and pediatric patients and healthy normal volunteers are summarized in Tables 14 and 16.

Table 14. Mean[a] Pharmacokinetic Parameters in Healthy Volunteers and Adult Patients With Epilepsy

Adult Study Population	Number of Subjects	T_{max}: Time of Maximum Plasma Concentration (hr)	$t_{½}$: Elimination Half-life (hr)	Cl/F: Apparent Plasma Clearance (mL/min/kg)
Healthy volunteers taking no other medications:				
Single-dose LAMICTAL	179	2.2 (0.25-12.0)	32.8 (14.0-103.0)	0.44 (0.12-1.10)
Multiple-dose LAMICTAL	36	1.7 (0.5-4.0)	25.4 (11.6-61.6)	0.58 (0.24-1.15)
Healthy volunteers taking valproate:				
Single-dose LAMICTAL	6	1.8 (1.0-4.0)	48.3 (31.5-88.6)	0.30 (0.14-0.42)
Multiple-dose LAMICTAL	18	1.9 (0.5-3.5)	70.3 (41.9-113.5)	0.18 (0.12-0.33)
Patients with epilepsy taking valproate only:				
Single-dose LAMICTAL	4	4.8 (1.8-8.4)	58.8 (30.5-88.8)	0.28 (0.16-0.40)
Patients with epilepsy taking carbamazepine, phenytoin, phenobarbital, or primidone[b] plus valproate:				
Single-dose LAMICTAL	25	3.8 (1.0-10.0)	27.2 (11.2-51.6)	0.53 (0.27-1.04)
Patients with epilepsy taking carbamazepine, phenytoin, phenobarbital, or primidone:[b]				
Single-dose LAMICTAL	24	2.3 (0.5-5.0)	14.4 (6.4-30.4)	1.10 (0.51-2.22)
Multiple-dose LAMICTAL	17	2.0 (0.75-5.93)	12.6 (7.5-23.1)	1.21 (0.66-1.82)

[a] The majority of parameter means determined in each study had coefficients of variation between 20% and 40% for half-life and Cl/F and between 30% and 70% for T_{max}. The overall mean values were calculated from individual study means that were weighted based on the

number of volunteers/patients in each study. The numbers in parentheses below each parameter mean represent the range of individual volunteer/patient values across studies.

[b] Carbamazepine, phenobarbital, phenytoin, and primidone have been shown to increase the apparent clearance of lamotrigine. Estrogen-containing oral contraceptives and other drugs such as rifampin that induce lamotrigine glucuronidation have also been shown to increase the apparent clearance of lamotrigine *[see Drug Interactions (7)]*.

Absorption: Lamotrigine is rapidly and completely absorbed after oral administration with negligible first-pass metabolism (absolute bioavailability is 98%). The bioavailability is not affected by food. Peak plasma concentrations occur anywhere from 1.4 to 4.8 hours following drug administration. The lamotrigine chewable/dispersible tablets were found to be equivalent, whether they were administered as dispersed in water, chewed and swallowed, or swallowed as whole, to the lamotrigine compressed tablets in terms of rate and extent of absorption. In terms of rate and extent of absorption, lamotrigine orally disintegrating tablets whether disintegrated in the mouth or swallowed whole with water were equivalent to the lamotrigine compressed tablets swallowed with water.

Dose Proportionality: In healthy volunteers not receiving any other medications and given single doses, the plasma concentrations of lamotrigine increased in direct proportion to the dose administered over the range of 50 to 400 mg. In 2 small studies (n = 7 and 8) of patients with epilepsy who were maintained on other AEDs, there also was a linear relationship between dose and lamotrigine plasma concentrations at steady state following doses of 50 to 350 mg twice daily.

Distribution: Estimates of the mean apparent volume of distribution (Vd/F) of lamotrigine following oral administration ranged from 0.9 to 1.3 L/kg. Vd/F is independent of dose and is similar following single and multiple doses in both patients with epilepsy and in healthy volunteers.

Protein Binding: Data from in vitro studies indicate that lamotrigine is approximately 55% bound to human plasma proteins at plasma lamotrigine concentrations from 1 to 10 mcg/mL (10 mcg/mL is 4 to 6 times the trough plasma concentration observed in the controlled efficacy trials). Because lamotrigine is not highly bound to plasma proteins, clinically significant interactions with other drugs through competition for protein binding sites are unlikely. The binding of lamotrigine to plasma proteins did not change in the presence of therapeutic concentrations of phenytoin, phenobarbital, or valproate. Lamotrigine did not displace other AEDs (carbamazepine, phenytoin, phenobarbital) from protein-binding sites.

Metabolism: Lamotrigine is metabolized predominantly by glucuronic acid conjugation; the major metabolite is an inactive 2-N-glucuronide conjugate. After oral administration of 240 mg of ^{14}C-lamotrigine (15 μCi) to 6 healthy volunteers, 94% was recovered in the urine and 2% was recovered in the feces. The radioactivity in the urine consisted of unchanged lamotrigine

(10%), the 2-N-glucuronide (76%), a 5-N-glucuronide (10%), a 2-N-methyl metabolite (0.14%), and other unidentified minor metabolites (4%).

Enzyme Induction: The effects of lamotrigine on the induction of specific families of mixed-function oxidase isozymes have not been systematically evaluated.

Following multiple administrations (150 mg twice daily) to normal volunteers taking no other medications, lamotrigine induced its own metabolism, resulting in a 25% decrease in $t_{½}$ and a 37% increase in Cl/F at steady state compared with values obtained in the same volunteers following a single dose. Evidence gathered from other sources suggests that self-induction by lamotrigine may not occur when lamotrigine is given as adjunctive therapy in patients receiving enzyme-inducing drugs such as carbamazepine, phenytoin, phenobarbital, primidone, or drugs such as rifampin that induce lamotrigine glucuronidation *[see Drug Interactions (7)*].

Elimination: The elimination half-life and apparent clearance of lamotrigine following administration of LAMICTAL to adult patients with epilepsy and healthy volunteers is summarized in Table 14. Half-life and apparent oral clearance vary depending on concomitant AEDs.

Drug Interactions: The apparent clearance of lamotrigine is affected by the coadministration of certain medications *[see Warnings and Precautions (5.9, 5.13), Drug Interactions (7)]*.

The net effects of drug interactions with LAMICTAL are summarized in Tables 13 and 15, followed by details of the drug interaction studies below.

Table 15. Summary of Drug Interactions With LAMICTAL

Drug	Drug Plasma Concentration With Adjunctive LAMICTAL[a]	Lamotrigine Plasma Concentration With Adjunctive Drugs[b]
Oral contraceptives (e.g., ethinylestradiol/levonorgestrel)[c]	↔[d]	↓
Bupropion	Not assessed	↔
Carbamazepine (CBZ)	↔	↓
CBZ epoxide[e]	?	
Felbamate	Not assessed	↔
Gabapentin	Not assessed	↔
Levetiracetam	↔	↔
Lithium	↔	Not assessed
Olanzapine	↔	↔[f]
Oxcarbazepine	↔	↔
10-monohydroxy oxcarbazepine metabolite[g]	↔	
Phenobarbital/primidone	↔	↓

Phenytoin (PHT)	↔	↓
Pregabalin	↔	↔
Rifampin	Not assessed	↓
Topiramate	↔[h]	↔
Valproate	↓	↑
Valproate + PHT and/or CBZ	Not assessed	↔
Zonisamide	Not assessed	↔

[a] From adjunctive clinical trials and volunteer studies.
[b] Net effects were estimated by comparing the mean clearance values obtained in adjunctive clinical trials and volunteer studies.
[c] The effect of other hormonal contraceptive preparations or hormone replacement therapy on the pharmacokinetics of lamotrigine has not been systematically evaluated in clinical trials, although the effect may be similar to that seen with the ethinylestradiol/levonorgestrel combinations.
[d] Modest decrease in levonorgestrel.
[e] Not administered, but an active metabolite of carbamazepine.
[f] Slight decrease, not expected to be clinically relevant.
[g] Not administered, but an active metabolite of oxcarbazepine.
[h] Slight increase, not expected to be clinically relevant.
↔ = No significant effect.
? = Conflicting data.

Estrogen-Containing Oral Contraceptives: In 16 female volunteers, an oral contraceptive preparation containing 30 mcg ethinylestradiol and 150 mcg levonorgestrel increased the apparent clearance of lamotrigine (300 mg/day) by approximately 2-fold with mean decreases in AUC of 52% and in C_{max} of 39%. In this study, trough serum lamotrigine concentrations gradually increased and were approximately 2-fold higher on average at the end of the week of the inactive hormone preparation compared with trough lamotrigine concentrations at the end of the active hormone cycle.

Gradual transient increases in lamotrigine plasma levels (approximate 2-fold increase) occurred during the week of inactive hormone preparation ("pill-free" week) for women not also taking a drug that increased the clearance of lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin that induce lamotrigine glucuronidation *[see Drug Interactions (7)]*). The increase in lamotrigine plasma levels will be greater if the dose of LAMICTAL is increased in the few days before or during the "pill-free" week. Increases in lamotrigine plasma levels could result in dose-dependent adverse reactions.

In the same study, coadministration of LAMICTAL (300 mg/day) in 16 female volunteers did not affect the pharmacokinetics of the ethinylestradiol component of the oral contraceptive preparation. There were mean decreases in the AUC and C_{max} of the levonorgestrel

component of 19% and 12%, respectively. Measurement of serum progesterone indicated that there was no hormonal evidence of ovulation in any of the 16 volunteers, although measurement of serum FSH, LH, and estradiol indicated that there was some loss of suppression of the hypothalamic-pituitary-ovarian axis.

The effects of doses of LAMICTAL other than 300 mg/day have not been systematically evaluated in controlled clinical trials.

The clinical significance of the observed hormonal changes on ovulatory activity is unknown. However, the possibility of decreased contraceptive efficacy in some patients cannot be excluded. Therefore, patients should be instructed to promptly report changes in their menstrual pattern (e.g., break-through bleeding).

Dosage adjustments may be necessary for women receiving estrogen-containing oral contraceptive preparations *[see Dosage and Administration (2.1)]*.

Other Hormonal Contraceptives 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.

Bupropion: The pharmacokinetics of a 100-mg single dose of LAMICTAL in healthy volunteers (n = 12) were not changed by coadministration of bupropion sustained-release formulation (150 mg twice daily) starting 11 days before LAMICTAL.

Carbamazepine: LAMICTAL has no appreciable effect on steady-state carbamazepine plasma concentration. Limited clinical data suggest there is a higher incidence of dizziness, diplopia, ataxia, and blurred vision in patients receiving carbamazepine with lamotrigine than in patients receiving other AEDs with lamotrigine *[see Adverse Reactions (6.1)]*. The mechanism of this interaction is unclear. The effect of lamotrigine on plasma concentrations of carbamazepine-epoxide is unclear. In a small subset of patients (n = 7) studied in a placebo-controlled trial, lamotrigine had no effect on carbamazepine-epoxide plasma concentrations, but in a small, uncontrolled study (n = 9), carbamazepine-epoxide levels increased.

The addition of carbamazepine decreases lamotrigine steady-state concentrations by approximately 40%.

Felbamate: In a study of 21 healthy volunteers, coadministration of felbamate (1,200 mg twice daily) with lamotrigine (100 mg twice daily for 10 days) appeared to have no clinically relevant effects on the pharmacokinetics of lamotrigine.

Folate Inhibitors: Lamotrigine is a weak inhibitor of dihydrofolate reductase. Prescribers should be aware of this action when prescribing other medications that inhibit folate metabolism.

Gabapentin: Based on a retrospective analysis of plasma levels in 34 patients who received lamotrigine both with and without gabapentin, gabapentin does not appear to change the apparent clearance of lamotrigine.

Levetiracetam: Potential drug interactions between levetiracetam and lamotrigine were assessed by evaluating serum concentrations of both agents during placebo-controlled clinical trials. These data indicate that lamotrigine does not influence the pharmacokinetics of levetiracetam and that levetiracetam does not influence the pharmacokinetics of lamotrigine.

Lithium: The pharmacokinetics of lithium were not altered in healthy subjects (n = 20) by coadministration of lamotrigine (100 mg/day) for 6 days.

Olanzapine: The AUC and C_{max} of olanzapine were similar following the addition of olanzapine (15 mg once daily) to lamotrigine (200 mg once daily) in healthy male volunteers (n = 16) compared with the AUC and C_{max} in healthy male volunteers receiving olanzapine alone (n = 16).

In the same study, the AUC and C_{max} of lamotrigine were reduced on average by 24% and 20%, respectively, following the addition of olanzapine to lamotrigine in healthy male volunteers compared with those receiving lamotrigine alone. This reduction in lamotrigine plasma concentrations is not expected to be clinically relevant.

Oxcarbazepine: The AUC and C_{max} of oxcarbazepine and its active 10-monohydroxy oxcarbazepine metabolite were not significantly different following the addition of oxcarbazepine (600 mg twice daily) to lamotrigine (200 mg once daily) in healthy male volunteers (n = 13) compared with healthy male volunteers receiving oxcarbazepine alone (n = 13).

In the same study, the AUC and C_{max} of lamotrigine were similar following the addition of oxcarbazepine (600 mg twice daily) to LAMICTAL in healthy male volunteers compared with those receiving LAMICTAL alone. Limited clinical data suggest a higher incidence of headache, dizziness, nausea, and somnolence with coadministration of lamotrigine and oxcarbazepine compared with lamotrigine alone or oxcarbazepine alone.

Phenobarbital, Primidone: The addition of phenobarbital or primidone decreases lamotrigine steady-state concentrations by approximately 40%.

Phenytoin: Lamotrigine has no appreciable effect on steady-state phenytoin plasma concentrations in patients with epilepsy. The addition of phenytoin decreases lamotrigine steady-state concentrations by approximately 40%.

Pregabalin: Steady-state trough plasma concentrations of lamotrigine were not affected by concomitant pregabalin (200 mg 3 times daily) administration. There are no pharmacokinetic interactions between lamotrigine and pregabalin.

Rifampin: In 10 male volunteers, rifampin (600 mg/day for 5 days) significantly increased the apparent clearance of a single 25-mg dose of lamotrigine by approximately 2-fold (AUC decreased by approximately 40%).

Topiramate: Topiramate resulted in no change in plasma concentrations of lamotrigine. Administration of lamotrigine resulted in a 15% increase in topiramate concentrations.

Valproate: When lamotrigine was administered to healthy volunteers (n = 18) receiving valproate, the trough steady-state valproate plasma concentrations decreased by an average of 25% over a 3-week period, and then stabilized. However, adding lamotrigine to the existing therapy did not cause a change in valproate plasma concentrations in either adult or pediatric patients in controlled clinical trials.

The addition of valproate increased lamotrigine steady-state concentrations in normal volunteers by slightly more than 2-fold. In one study, maximal inhibition of lamotrigine clearance was reached at valproate doses between 250 and 500 mg/day and did not increase as the valproate dose was further increased.

Zonisamide: In a study of 18 patients with epilepsy, coadministration of zonisamide (200 to 400 mg/day) with lamotrigine (150 to 500 mg/day for 35 days) had no significant effect on the pharmacokinetics of lamotrigine.

Known Inducers or Inhibitors of Glucuronidation: Drugs other than those listed above have not been systematically evaluated in combination with lamotrigine. Since lamotrigine is metabolized predominately by glucuronic acid conjugation, drugs that are known to induce or inhibit glucuronidation may affect the apparent clearance of lamotrigine and doses of lamotrigine may require adjustment based on clinical response.

Other: Results of in vitro experiments suggest that clearance of lamotrigine is unlikely to be reduced by concomitant administration of amitriptyline, clonazepam, clozapine, fluoxetine, haloperidol, lorazepam, phenelzine, risperidone, sertraline, or trazodone.

Results of in vitro experiments suggest that lamotrigine does not reduce the clearance of drugs eliminated predominantly by CYP2D6.

Special Populations: *Patients With Renal Impairment:* Twelve volunteers with chronic renal failure (mean creatinine clearance: 13 mL/min; range: 6 to 23) and another 6 individuals undergoing hemodialysis were each given a single 100-mg dose of lamotrigine. The mean plasma half-lives determined in the study were 42.9 hours (chronic renal failure), 13.0 hours (during hemodialysis), and 57.4 hours (between hemodialysis) compared with 26.2 hours in healthy volunteers. On average, approximately 20% (range: 5.6 to 35.1) of the amount of lamotrigine present in the body was eliminated by hemodialysis during a 4-hour session *[see Dosage and Administration (2.1)]*.

Hepatic Disease: The pharmacokinetics of lamotrigine following a single 100-mg dose of lamotrigine were evaluated in 24 subjects with mild, moderate, and severe hepatic impairment (Child-Pugh Classification system) and compared with 12 subjects without hepatic impairment. The patients with severe hepatic impairment were without ascites (n = 2) or with ascites (n = 5). The mean apparent clearances of lamotrigine in patients with mild (n = 12), moderate (n = 5), severe without ascites (n = 2), and severe with ascites (n = 5) liver impairment were 0.30 ± 0.09, 0.24 ± 0.1, 0.21 ± 0.04, and 0.15 ± 0.09 mL/min/kg, respectively, as compared

with 0.37 ± 0.1 mL/min/kg in the healthy controls. Mean half-lives of lamotrigine in patients with mild, moderate, severe without ascites, and severe with ascites hepatic impairment were 46 ± 20, 72 ± 44, 67 ± 11, and 100 ± 48 hours, respectively, as compared with 33 ± 7 hours in healthy controls *[see Dosage and Administration (2.1)]*.

Age: Pediatric Patients: The pharmacokinetics of lamotrigine following a single 2-mg/kg dose were evaluated in 2 studies of pediatric patients (n = 29 for patients 10 months to 5.9 years of age and n = 26 for patients 5 to 11 years of age). Forty-three patients received concomitant therapy with other AEDs and 12 patients received lamotrigine as monotherapy. Lamotrigine pharmacokinetic parameters for pediatric patients are summarized in Table 16.

Population pharmacokinetic analyses involving patients 2 to 18 years of age demonstrated that lamotrigine clearance was influenced predominantly by total body weight and concurrent AED therapy. The oral clearance of lamotrigine was higher, on a body weight basis, in pediatric patients than in adults. Weight-normalized lamotrigine clearance was higher in those subjects weighing less than 30 kg, compared with those weighing greater than 30 kg. Accordingly, patients weighing less than 30 kg may need an increase of as much as 50% in maintenance doses, based on clinical response, as compared with subjects weighing more than 30 kg being administered the same AEDs *[see Dosage and Administration (2.2)]*. These analyses also revealed that, after accounting for body weight, lamotrigine clearance was not significantly influenced by age. Thus, the same weight-adjusted doses should be administered to children irrespective of differences in age. Concomitant AEDs which influence lamotrigine clearance in adults were found to have similar effects in children.

Table 16. Mean Pharmacokinetic Parameters in Pediatric Patients With Epilepsy

Pediatric Study Population	Number of Subjects	T_{max} (hr)	$t_{½}$ (hr)	Cl/F (mL/min/kg)
Ages 10 months-5.3 years				
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone[a]	10	3.0 (1.0-5.9)	7.7 (5.7-11.4)	3.62 (2.44-5.28)
Patients taking AEDs with no known effect on the apparent clearance of lamotrigine	7	5.2 (2.9-6.1)	19.0 (12.9-27.1)	1.2 (0.75-2.42)
Patients taking valproate only	8	2.9 (1.0-6.0)	44.9 (29.5-52.5)	0.47 (0.23-0.77)
Ages 5-11 years				
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone[a]	7	1.6 (1.0-3.0)	7.0 (3.8-9.8)	2.54 (1.35-5.58)

Patients taking carbamazepine, phenytoin, phenobarbital, or primidone[a] plus valproate	8	3.3 (1.0-6.4)	19.1 (7.0-31.2)	0.89 (0.39-1.93)
Patients taking valproate only[b]	3	4.5 (3.0-6.0)	65.8 (50.7-73.7)	0.24 (0.21-0.26)
Ages 13-18 years				
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone[a]	11	[c]	[c]	1.3
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone[a] plus valproate	8	[c]	[c]	0.5
Patients taking valproate only	4	[c]	[c]	0.3

[a] Carbamazepine, phenobarbital, phenytoin, and primidone have been shown to increase the apparent clearance of lamotrigine. Estrogen-containing oral contraceptives and rifampin have also been shown to increase the apparent clearance of lamotrigine *[see Drug Interactions (7)]*.

[b] Two subjects were included in the calculation for mean T_{max}

[c] Parameter not estimated.

Elderly: The pharmacokinetics of lamotrigine following a single 150-mg dose of LAMICTAL were evaluated in 12 elderly volunteers between the ages of 65 and 76 years (mean creatinine clearance = 61 mL/min, range: 33 to 108 mL/min). The mean half-life of lamotrigine in these subjects was 31.2 hours (range: 24.5 to 43.4 hours), and the mean clearance was 0.40 mL/min/kg (range: 0.26 to 0.48 mL/min/kg).

Gender: The clearance of lamotrigine is not affected by gender. However, during dose escalation of LAMICTAL in one clinical trial in patients with epilepsy on a stable dose of valproate (n = 77), mean trough lamotrigine concentrations, unadjusted for weight, were 24% to 45% higher (0.3 to 1.7 mcg/mL) in females than in males.

Race: The apparent oral clearance of lamotrigine was 25% lower in non-Caucasians than Caucasians.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenicity was seen in 1 mouse study or 2 rat studies following oral administration of lamotrigine for up to 2 years at maximum tolerated doses (30 mg/kg/day for mice and 10 to 15 mg/kg/day for rats, doses that are equivalent to 90 mg/m^2 and 60 to 90 mg/m^2, respectively). Steady-state plasma concentrations ranged from 1 to 4 mcg/mL in the mouse study and 1 to 10 mcg/mL in the rat study. Plasma concentrations associated with the recommended

human doses of 300 to 500 mg/day are generally in the range of 2 to 5 mcg/mL, but concentrations as high as 19 mcg/mL have been recorded.

Lamotrigine was not mutagenic in the presence or absence of metabolic activation when tested in 2 gene mutation assays (the Ames test and the in vitro mammalian mouse lymphoma assay). In 2 cytogenetic assays (the in vitro human lymphocyte assay and the in vivo rat bone marrow assay), lamotrigine did not increase the incidence of structural or numerical chromosomal abnormalities.

No evidence of impairment of fertility was detected in rats given oral doses of lamotrigine up to 2.4 times the highest usual human maintenance dose of 8.33 mg/kg/day or 0.4 times the human dose on a mg/m^2 basis. The effect of lamotrigine on human fertility is unknown.

14 CLINICAL STUDIES

14.1 Epilepsy

Monotherapy With LAMICTAL in Adults With Partial Seizures Already Receiving Treatment With Carbamazepine, Phenytoin, Phenobarbital, or Primidone as the Single AED: The effectiveness of monotherapy with LAMICTAL was established in a multicenter, double-blind clinical trial enrolling 156 adult outpatients with partial seizures. The patients experienced at least 4 simple partial, complex partial, and/or secondarily generalized seizures during each of 2 consecutive 4-week periods while receiving carbamazepine or phenytoin monotherapy during baseline. LAMICTAL (target dose of 500 mg/day) or valproate (1,000 mg/day) was added to either carbamazepine or phenytoin monotherapy over a 4-week period. Patients were then converted to monotherapy with LAMICTAL or valproate during the next 4 weeks, then continued on monotherapy for an additional 12-week period.

Study endpoints were completion of all weeks of study treatment or meeting an escape criterion. Criteria for escape relative to baseline were: (1) doubling of average monthly seizure count, (2) doubling of highest consecutive 2-day seizure frequency, (3) emergence of a new seizure type (defined as a seizure that did not occur during the 8-week baseline) that is more severe than seizure types that occur during study treatment, or (4) clinically significant prolongation of generalized tonic-clonic (GTC) seizures. The primary efficacy variable was the proportion of patients in each treatment group who met escape criteria.

The percentages of patients who met escape criteria were 42% (32/76) in the group receiving LAMICTAL and 69% (55/80) in the valproate group. The difference in the percentage of patients meeting escape criteria was statistically significant (p= 0.0012) in favor of LAMICTAL. No differences in efficacy based on age, sex, or race were detected.

Patients in the control group were intentionally treated with a relatively low dose of valproate; as such, the sole objective of this study was to demonstrate the effectiveness and safety of monotherapy with LAMICTAL, and cannot be interpreted to imply the superiority of LAMICTAL to an adequate dose of valproate.

Adjunctive Therapy With LAMICTAL in Adults With Partial Seizures: The effectiveness of LAMICTAL as adjunctive therapy (added to other AEDs) was established in 3 multicenter, placebo-controlled, double-blind clinical trials in 355 adults with refractory partial seizures. The patients had a history of at least 4 partial seizures per month in spite of receiving one or more AEDs at therapeutic concentrations and, in 2 of the studies, were observed on their established AED regimen during baselines that varied between 8 to 12 weeks. In the third, patients were not observed in a prospective baseline. In patients continuing to have at least 4 seizures per month during the baseline, LAMICTAL or placebo was then added to the existing therapy. In all 3 studies, change from baseline in seizure frequency was the primary measure of effectiveness. The results given below are for all partial seizures in the intent-to-treat population (all patients who received at least one dose of treatment) in each study, unless otherwise indicated. The median seizure frequency at baseline was 3 per week while the mean at baseline was 6.6 per week for all patients enrolled in efficacy studies.

One study (n = 216) was a double-blind, placebo-controlled, parallel trial consisting of a 24-week treatment period. Patients could not be on more than 2 other anticonvulsants and valproate was not allowed. Patients were randomized to receive placebo, a target dose of 300 mg/day of LAMICTAL, or a target dose of 500 mg/day of LAMICTAL. The median reductions in the frequency of all partial seizures relative to baseline were 8% in patients receiving placebo, 20% in patients receiving 300 mg/day of LAMICTAL, and 36% in patients receiving 500 mg/day of LAMICTAL. The seizure frequency reduction was statistically significant in the 500-mg/day group compared with the placebo group, but not in the 300-mg/day group.

A second study (n = 98) was a double-blind, placebo-controlled, randomized, crossover trial consisting of two 14-week treatment periods (the last 2 weeks of which consisted of dose tapering) separated by a 4-week washout period. Patients could not be on more than 2 other anticonvulsants and valproate was not allowed. The target dose of LAMICTAL was 400 mg/day. When the first 12 weeks of the treatment periods were analyzed, the median change in seizure frequency was a 25% reduction on LAMICTAL compared with placebo ($p<0.001$).

The third study (n = 41) was a double-blind, placebo-controlled, crossover trial consisting of two 12-week treatment periods separated by a 4-week washout period. Patients could not be on more than 2 other anticonvulsants. Thirteen patients were on concomitant valproate; these patients received 150 mg/day of LAMICTAL. The 28 other patients had a target dose of 300 mg/day of LAMICTAL. The median change in seizure frequency was a 26% reduction on LAMICTAL compared with placebo ($p<0.01$).

No differences in efficacy based on age, sex, or race, as measured by change in seizure frequency, were detected.

Adjunctive Therapy With LAMICTAL in Pediatric Patients With Partial Seizures: The effectiveness of LAMICTAL as adjunctive therapy in pediatric patients with partial seizures was established in a multicenter, double-blind, placebo-controlled trial in 199 patients 2 to 16

years of age (n = 98 on LAMICTAL, n = 101 on placebo). Following an 8-week baseline phase, patients were randomized to 18 weeks of treatment with LAMICTAL or placebo added to their current AED regimen of up to 2 drugs. Patients were dosed based on body weight and valproate use. Target doses were designed to approximate 5 mg/kg/day for patients taking valproate (maximum dose: 250 mg/day) and 15 mg/kg/day for the patients not taking valproate (maximum dose: 750 mg/day). The primary efficacy endpoint was percentage change from baseline in all partial seizures. For the intent-to-treat population, the median reduction of all partial seizures was 36% in patients treated with LAMICTAL and 7% on placebo, a difference that was statistically significant ($p<0.01$).

Adjunctive Therapy With LAMICTAL in Pediatric and Adult Patients With Lennox-Gastaut Syndrome: The effectiveness of LAMICTAL as adjunctive therapy in patients with Lennox-Gastaut syndrome was established in a multicenter, double-blind, placebo-controlled trial in 169 patients 3 to 25 years of age (n = 79 on LAMICTAL, n = 90 on placebo). Following a 4-week single-blind, placebo phase, patients were randomized to 16 weeks of treatment with LAMICTAL or placebo added to their current AED regimen of up to 3 drugs. Patients were dosed on a fixed-dose regimen based on body weight and valproate use. Target doses were designed to approximate 5 mg/kg/day for patients taking valproate (maximum dose: 200 mg/day) and 15 mg/kg/day for patients not taking valproate (maximum dose: 400 mg/day). The primary efficacy endpoint was percentage change from baseline in major motor seizures (atonic, tonic, major myoclonic, and tonic-clonic seizures). For the intent-to-treat population, the median reduction of major motor seizures was 32% in patients treated with LAMICTAL and 9% on placebo, a difference that was statistically significant ($p<0.05$). Drop attacks were significantly reduced by LAMICTAL (34%) compared with placebo (9%), as were tonic-clonic seizures (36% reduction versus 10% increase for LAMICTAL and placebo, respectively).

Adjunctive Therapy With LAMICTAL in Pediatric and Adult Patients With Primary Generalized Tonic-Clonic Seizures: The effectiveness of LAMICTAL as adjunctive therapy in patients with primary generalized tonic-clonic seizures was established in a multicenter, double-blind, placebo-controlled trial in 117 pediatric and adult patients ≥2 years (n = 58 on LAMICTAL, n = 59 on placebo). Patients with at least 3 primary generalized tonic-clonic seizures during an 8-week baseline phase were randomized to 19 to 24 weeks of treatment with LAMICTAL or placebo added to their current AED regimen of up to 2 drugs. Patients were dosed on a fixed-dose regimen, with target doses ranging from 3 mg/kg/day to 12 mg/kg/day for pediatric patients and from 200 mg/day to 400 mg/day for adult patients based on concomitant AED.

The primary efficacy endpoint was percentage change from baseline in primary generalized tonic-clonic seizures. For the intent-to-treat population, the median percent reduction of primary generalized tonic-clonic seizures was 66% in patients treated with LAMICTAL and 34% on placebo, a difference that was statistically significant ($p = 0.006$).

14.2 Bipolar Disorder

The effectiveness of LAMICTAL in the maintenance treatment of Bipolar I Disorder was established in 2 multicenter, double-blind, placebo-controlled studies in adult patients who met DSM-IV criteria for Bipolar I Disorder. Study 1 enrolled patients with a current or recent (within 60 days) depressive episode as defined by DSM-IV and Study 2 included patients with a current or recent (within 60 days) episode of mania or hypomania as defined by DSM-IV. Both studies included a cohort of patients (30% of 404 patients in Study 1 and 28% of 171 patients in Study 2) with rapid cycling Bipolar Disorder (4 to 6 episodes per year).

In both studies, patients were titrated to a target dose of 200 mg of LAMICTAL, as add-on therapy or as monotherapy, with gradual withdrawal of any psychotropic medications during an 8- to 16-week open-label period. Overall 81% of 1,305 patients participating in the open-label period were receiving 1 or more other psychotropic medications, including benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), atypical antipsychotics (including olanzapine), valproate, or lithium, during titration of LAMICTAL. Patients with a CGI-severity score of 3 or less maintained for at least 4 continuous weeks, including at least the final week on monotherapy with LAMICTAL, were randomized to a placebo-controlled, double-blind treatment period for up to 18 months. The primary endpoint was TIME (time to intervention for a mood episode or one that was emerging, time to discontinuation for either an adverse event that was judged to be related to Bipolar Disorder, or for lack of efficacy). The mood episode could be depression, mania, hypomania, or a mixed episode.

In Study 1, patients received double-blind monotherapy with LAMICTAL 50 mg/day (n = 50), LAMICTAL 200 mg/day (n = 124), LAMICTAL 400 mg/day (n = 47), or placebo (n = 121). LAMICTAL (200- and 400-mg/day treatment groups combined) was superior to placebo in delaying the time to occurrence of a mood episode. Separate analyses of the 200- and 400-mg/day dose groups revealed no added benefit from the higher dose.

In Study 2, patients received double-blind monotherapy with LAMICTAL (100 to 400 mg/day, n = 59), or placebo (n = 70). LAMICTAL was superior to placebo in delaying time to occurrence of a mood episode. The mean dose of LAMICTAL was about 211 mg/day.

Although these studies were not designed to separately evaluate time to the occurrence of depression or mania, a combined analysis for the 2 studies revealed a statistically significant benefit for LAMICTAL over placebo in delaying the time to occurrence of both depression and mania, although the finding was more robust for depression.

16 HOW SUPPLIED/STORAGE AND HANDLING

LAMICTAL (lamotrigine) Tablets

25 mg, white, scored, shield-shaped tablets debossed with “LAMICTAL” and “25”, bottles of 100 (NDC 0173-0633-02).

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

100 mg, peach, scored, shield-shaped tablets debossed with “LAMICTAL” and “100”, bottles of 100 (NDC 0173-0642-55).

150 mg, cream, scored, shield-shaped tablets debossed with “LAMICTAL” and “150”, bottles of 60 (NDC 0173-0643-60).

200 mg, blue, scored, shield-shaped tablets debossed with “LAMICTAL” and “200”, bottles of 60 (NDC 0173-0644-60).

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature] in a dry place and protect from light.

LAMICTAL (lamotrigine) Starter Kit for Patients Taking Valproate (Blue Kit)

25 mg, white, scored, shield-shaped tablets debossed with “LAMICTAL” and “25”, blisterpack of 35 tablets (NDC 0173-0633-10).

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

LAMICTAL (lamotrigine) Starter Kit for Patients Taking Carbamazepine, Phenytoin, Phenobarbital, or Primidone and Not Taking Valproate (Green Kit)

25 mg, white, scored, shield-shaped tablets debossed with “LAMICTAL” and “25” and 100 mg, peach, scored, shield-shaped tablets debossed with “LAMICTAL” and “100”, blisterpack of 98 tablets (84/25-mg tablets and 14/100-mg tablets) (NDC 0173-0817-28).

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature] in a dry place and protect from light.

LAMICTAL (lamotrigine) Starter Kit for Patients Not Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate (Orange Kit)

25 mg, white, scored, shield-shaped tablets debossed with “LAMICTAL” and “25” and 100 mg, peach, scored, shield-shaped tablets debossed with “LAMICTAL” and “100”, blisterpack of 49 tablets (42/25-mg tablets and 7/100-mg tablets) (NDC 0173-0594-02).

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature] in a dry place and protect from light.

LAMICTAL (lamotrigine) Chewable Dispersible Tablets

2 mg, white to off-white, round tablets debossed with “LTG” over “2”, bottles of 30 (NDC 0173-0699-00). ORDER DIRECTLY FROM GlaxoSmithKline 1-800-334-4153.

5 mg, white to off-white, caplet-shaped tablets debossed with “GX CL2”, bottles of 100 (NDC 0173-0526-00).

25 mg, white, super elliptical-shaped tablets debossed with “GX CL5”, bottles of 100 (NDC 0173-0527-00).

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

LAMICTAL ODT (lamotrigine) Orally Disintegrating Tablets

25 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with "LMT" on one side and "25" on the other, Maintenance Packs of 30 (NDC 0173-0772-02).

50 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with "LMT" on one side and "50" on the other, Maintenance Packs of 30 (NDC 0173-0774-02).

100 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with "LAMICTAL" on one side and "100" on the other, Maintenance Packs of 30 (NDC 0173-0776-02).

200 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with "LAMICTAL" on one side and "200" on the other, Maintenance Packs of 30 (NDC 0173-0777-02).

Store between 20°C to 25°C (68°F to 77°F); with excursions permitted between 15°C and 30°C (59°F and 86°F).

LAMICTAL ODT (lamotrigine) Patient Titration Kit for Patients Taking Valproate (Blue ODT Kit)

25 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with "LMT" on one side and "25" on the other, and 50 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with "LMT" on one side and "50" on the other, blisterpack of 28 tablets (21/25-mg tablets and 7/50-mg tablets) (NDC 0173-0779-00).

LAMICTAL ODT (lamotrigine) Patient Titration Kit for Patients Taking Carbamazepine, Phenytoin, Phenobarbital, or Primidone and Not Taking Valproate (Green ODT Kit)

50 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with "LMT" on one side and "50" on the other, and 100 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with "LAMICTAL" on one side and "100" on the other, blisterpack of 56 tablets (42/50-mg tablets and 14/100-mg tablets) (NDC 0173-0780-00).

LAMICTAL ODT (lamotrigine) Patient Titration Kit for Patients Not Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate (Orange ODT Kit)

25 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with "LMT" on one side and "25" on the other, 50 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with "LMT" on one side and "50" on the other, and 100 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with "LAMICTAL" on one side and "100" on the other, blisterpack of 35 (14/25-mg tablets, 14/50-mg tablets, and 7/100-mg tablets) (NDC 0173-0778-00).

Store between 20°C to 25°C (68°F to 77°F); with excursions permitted between 15°C and 30°C (59°F and 86°F).

Blisterpacks: If the product is dispensed in a blisterpack, the patient should be advised to examine the blisterpack before use and not use if blisters are torn, broken, or missing.

17 PATIENT COUNSELING INFORMATION

See Medication Guide that accompanies the product.

17.1 Rash

Prior to initiation of treatment with LAMICTAL, the patient should be instructed that a rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy) may herald a serious medical event and that the patient should report any such occurrence to a physician immediately.

17.2 Suicidal Thinking and Behavior

Patients, their caregivers, and families should be counseled that AEDs, including LAMICTAL, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

17.3 Worsening of Seizures

Patients should be advised to notify their physician if worsening of seizure control occurs.

17.4 CNS Adverse Effects

Patients should be advised that LAMICTAL may cause dizziness, somnolence, and other symptoms and signs of central nervous system (CNS) depression. Accordingly, they should be advised neither to drive a car nor to operate other complex machinery until they have gained sufficient experience on LAMICTAL to gauge whether or not it adversely affects their mental and/or motor performance.

17.5 Blood Dyscrasias and/or Acute Multiorgan Failure

Patients should be advised of the possibility of blood dyscrasias and/or acute multiorgan failure and to contact their physician immediately if they experience any signs or symptoms of these conditions *[see Warnings and Precautions (5.3, 5.4)]*.

17.6 Pregnancy

Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy. Patients should be advised to notify their physicians if they intend to breastfeed or are breastfeeding an infant.

Patients should also be encouraged to enroll in the NAAED Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll-free number 1-888-233-2334 *[see Use in Specific Populations (8.1)]*.

17.7 Oral Contraceptive Use

Women should be advised to notify their physician if they plan to start or stop use of oral contraceptives or other female hormonal preparations. Starting estrogen-containing oral contraceptives may significantly decrease lamotrigine plasma levels and stopping estrogen-containing oral contraceptives (including the “pill-free” week) may significantly increase lamotrigine plasma levels *[see Warnings and Precautions (5.9), Clinical Pharmacology (12.3)]*. Women should also be advised to promptly notify their physician if they experience adverse

reactions or changes in menstrual pattern (e.g., break-through bleeding) while receiving LAMICTAL in combination with these medications.

17.8 Discontinuing LAMICTAL

Patients should be advised to notify their physician if they stop taking LAMICTAL for any reason and not to resume LAMICTAL without consulting their physician.

17.9 Aseptic Meningitis

Patients should be advised that LAMICTAL may cause aseptic meningitis. Patients should be advised to notify their physician immediately if they develop signs and symptoms of meningitis such as headache, fever, nausea, vomiting, stiff neck, rash, abnormal sensitivity to light, myalgia, chills, confusion, or drowsiness while taking LAMICTAL.

17.10 Potential Medication Errors

Medication errors involving LAMICTAL have occurred. In particular the names LAMICTAL or lamotrigine can be confused with the names of other commonly used medications. Medication errors may also occur between the different formulations of LAMICTAL. To reduce the potential of medication errors, write and say LAMICTAL clearly. Depictions of the LAMICTAL Tablets, Chewable Dispersible Tablets, and Orally Disintegrating Tablets can be found in the Medication Guide that accompanies the product to highlight the distinctive markings, colors, and shapes that serve to identify the different presentations of the drug and thus may help reduce the risk of medication errors. **To avoid a medication error of using the wrong drug or formulation, patients should be strongly advised to visually inspect their tablets to verify that they are LAMICTAL, as well as the correct formulation of LAMICTAL, each time they fill their prescription** *[see Dosage Forms and Strengths (3.1, 3.2, 3.3), How Supplied/Storage and Handling (16)]*.

GlaxoSmithKline
Research Triangle Park, NC 27709

LAMICTAL Tablets and Chewable Dispersible Tablets are manufactured by
DSM Pharmaceuticals, Inc., Greenville, NC 27834 or
GlaxoSmithKline, Research Triangle Park, NC 27709
LAMICTAL Orally Disintegrating Tablets are manufactured by
Eurand, Inc., Vandalia, OH 45377

LMT:xPI