

## 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, Multiorgan Hypersensitivity Reactions and Organ Failure (5.2) August 2011

### INDICATIONS AND USAGE

LAMICTAL is an antiepileptic drug (AED) indicated for:

**Epilepsy—adjunctive therapy in patients  $\geq 2$  years of age:** (1.1)

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

**Epilepsy—monotherapy in patients  $\geq 16$  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  $\geq 18$  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, 5.8)
- LAMICTAL should be discontinued over a period of at least 2 weeks (approximately 50% reduction per week). (2.1, 5.9)

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

### ADVERSE REACTIONS

- Most common adverse reactions (incidence  $\geq 10\%$ ) in adult epilepsy clinical studies were dizziness, headache, diplopia, ataxia, nausea, blurred vision, somnolence, rhinitis, and rash. Additional adverse reactions (incidence  $\geq 10\%$ ) 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](http://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: 12/2013

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### WARNING: SERIOUS SKIN RASHES

#### 1 INDICATIONS AND USAGE

- 1.1 Epilepsy
- 1.2 Bipolar Disorder

#### 2 DOSAGE AND ADMINISTRATION

- 2.1 General Dosing Considerations
- 2.2 Epilepsy – Adjunctive Therapy
- 2.3 Epilepsy – Conversion From Adjunctive Therapy to Monotherapy

- 2.4 Bipolar Disorder
- 2.5 Administration of LAMICTAL Chewable Dispersible Tablets
- 2.6 Administration of LAMICTAL ODT Orally Disintegrating Tablets
- 3 DOSAGE FORMS AND STRENGTHS**
  - 3.1 Tablets
  - 3.2 Chewable Dispersible Tablets
  - 3.3 Orally Disintegrating Tablets
  - 3.4 Potential Medication Errors
- 4 CONTRAINDICATIONS**
- 5 WARNINGS AND PRECAUTIONS**
  - 5.1 Serious Skin Rashes [see Boxed Warning]
  - 5.2 Multiorgan Hypersensitivity Reactions and Organ Failure
  - 5.3 Blood Dyscrasias
  - 5.4 Suicidal Behavior and Ideation
  - 5.5 Use in Patients With Bipolar Disorder
  - 5.6 Aseptic Meningitis
  - 5.7 Potential Medication Errors
  - 5.8 Concomitant Use With Oral Contraceptives
  - 5.9 Withdrawal Seizures
  - 5.10 Status Epilepticus
  - 5.11 Sudden Unexplained Death in Epilepsy (SUDEP)
  - 5.12 Addition of LAMICTAL to a Multidrug Regimen That Includes Valproate
  - 5.13 Binding in the Eye and Other Melanin-Containing Tissues
  - 5.14 Laboratory Tests
- 6 ADVERSE REACTIONS**
  - 6.1 Clinical Trials
  - 6.2 Other Adverse Reactions Observed in All Clinical Trials
  - 6.3 Postmarketing Experience

- 7 DRUG INTERACTIONS**
- 8 USE IN SPECIFIC POPULATIONS**
  - 8.1 Pregnancy
  - 8.2 Labor and Delivery
  - 8.3 Nursing Mothers
  - 8.4 Pediatric Use
  - 8.5 Geriatric Use
  - 8.6 Patients With Hepatic Impairment
  - 8.7 Patients With Renal Impairment
- 10 OVERDOSAGE**
  - 10.1 Human Overdose Experience
  - 10.2 Management of Overdose
- 11 DESCRIPTION**
- 12 CLINICAL PHARMACOLOGY**
  - 12.1 Mechanism of Action
  - 12.2 Pharmacodynamics
  - 12.3 Pharmacokinetics
- 13 NONCLINICAL TOXICOLOGY**
  - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 14 CLINICAL STUDIES**
  - 14.1 Epilepsy
  - 14.2 Bipolar Disorder
- 16 HOW SUPPLIED/STORAGE AND HANDLING**
- 17 PATIENT COUNSELING INFORMATION**
  - 17.1 Rash
  - 17.2 Multiorgan Hypersensitivity Reactions, Blood Dyscrasias, and Organ Failure
  - 17.3 Suicidal Thinking and Behavior
  - 17.4 Worsening of Seizures
  - 17.5 Central Nervous System Adverse Effects
  - 17.6 Pregnancy and Nursing
  - 17.7 Oral Contraceptive Use
  - 17.8 Discontinuing LAMICTAL
  - 17.9 Aseptic Meningitis
  - 17.10 Potential Medication Errors

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

## 1 FULL PRESCRIBING INFORMATION

### 2 **WARNING: SERIOUS SKIN RASHES**

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

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

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

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

## 30 **1 INDICATIONS AND USAGE**

### 31 **1.1 Epilepsy**

32 **Adjunctive Therapy: LAMICTAL is indicated as adjunctive therapy for the following**  
33 **seizure types in patients  $\geq 2$  years of age:**

- 34 • partial seizures
- 35 • primary generalized tonic-clonic seizures
- 36 • generalized seizures of Lennox-Gastaut syndrome

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

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

## 44 **1.2 Bipolar Disorder**

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

49           The effectiveness of LAMICTAL as maintenance treatment was established in 2 placebo-  
50 controlled trials in patients with Bipolar I Disorder as defined by DSM-IV [*see Clinical Studies*  
51 (14.2)]. The physician who elects to prescribe LAMICTAL for periods extending beyond 16  
52 weeks should periodically re-evaluate the long-term usefulness of the drug for the individual  
53 patient.

## 54 **2 DOSAGE AND ADMINISTRATION**

### 55 **2.1 General Dosing Considerations**

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

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

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

72           It is recommended that LAMICTAL not be restarted in patients who discontinued due to  
73 rash associated with prior treatment with lamotrigine, unless the potential benefits clearly  
74 outweigh the risks. If the decision is made to restart a patient who has discontinued lamotrigine,  
75 the need to restart with the initial dosing recommendations should be assessed. The greater the

76 interval of time since the previous dose, the greater consideration should be given to restarting  
77 with the initial dosing recommendations. If a patient has discontinued lamotrigine for a period of  
78 more than 5 half-lives, it is recommended that initial dosing recommendations and guidelines be  
79 followed. The half-life of lamotrigine is affected by other concomitant medications [*see Clinical*  
80 *Pharmacology (12.3)*].

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

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

90 **Women Taking Estrogen-Containing Oral Contraceptives: Starting LAMICTAL in**  
91 ***Women Taking Estrogen-Containing Oral Contraceptives:*** Although estrogen-containing  
92 oral contraceptives have been shown to increase the clearance of lamotrigine [*see Clinical*  
93 *Pharmacology (12.3)*], no adjustments to the recommended dose-escalation guidelines for  
94 LAMICTAL should be necessary solely based on the use of estrogen-containing oral  
95 contraceptives. Therefore, dose escalation should follow the recommended guidelines for  
96 initiating adjunctive therapy with LAMICTAL based on the concomitant AED or other  
97 concomitant medications (see Table 1 or Table 5). See below for adjustments to maintenance  
98 doses of LAMICTAL in women taking estrogen-containing oral contraceptives.

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

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

107 (2) ***Starting Estrogen-Containing Oral Contraceptives:*** In women taking a  
108 stable dose of LAMICTAL and not taking carbamazepine, phenytoin, phenobarbital, primidone,  
109 or other drugs such as rifampin that induce lamotrigine glucuronidation [*see Drug Interactions*  
110 *(7), Clinical Pharmacology (12.3)*], the maintenance dose will in most cases need to be increased  
111 by as much as 2-fold in order to maintain a consistent lamotrigine plasma level. The dose  
112 increases should begin at the same time that the oral contraceptive is introduced and continue,  
113 based on clinical response, no more rapidly than 50 to 100 mg/day every week. Dose increases  
114 should not exceed the recommended rate (see Table 1 or Table 5) unless lamotrigine plasma

115 levels or clinical response support larger increases. Gradual transient increases in lamotrigine  
116 plasma levels may occur during the week of inactive hormonal preparation (“pill-free” week),  
117 and these increases will be greater if dose increases are made in the days before or during the  
118 week of inactive hormonal preparation. Increased lamotrigine plasma levels could result in  
119 additional adverse reactions, such as dizziness, ataxia, and diplopia. If adverse reactions  
120 attributable to LAMICTAL consistently occur during the “pill-free” week, dose adjustments to  
121 the overall maintenance dose may be necessary. Dose adjustments limited to the “pill-free” week  
122 are not recommended. For women taking LAMICTAL in addition to carbamazepine, phenytoin,  
123 phenobarbital, primidone, or other drugs such as rifampin that induce lamotrigine  
124 glucuronidation [*see Drug Interactions (7), Clinical Pharmacology (12.3)*], no adjustment to the  
125 dose of LAMICTAL should be necessary.

126 **(3) Stopping Estrogen-Containing Oral Contraceptives:** For women not  
127 taking carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin that  
128 induce lamotrigine glucuronidation [*see Drug Interactions (7), Clinical Pharmacology (12.3)*],  
129 the maintenance dose of LAMICTAL will in most cases need to be decreased by as much as  
130 50% in order to maintain a consistent lamotrigine plasma level. The decrease in dose of  
131 LAMICTAL should not exceed 25% of the total daily dose per week over a 2-week period,  
132 unless clinical response or lamotrigine plasma levels indicate otherwise [*see Clinical*  
133 *Pharmacology (12.3)*]. For women taking LAMICTAL in addition to carbamazepine, phenytoin,  
134 phenobarbital, primidone, or other drugs such as rifampin that induce lamotrigine  
135 glucuronidation [*see Drug Interactions (7), Clinical Pharmacology (12.3)*], no adjustment to the  
136 dose of LAMICTAL should be necessary.

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

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

152 **Patients With Renal Impairment:** Initial doses of LAMICTAL should be based on  
153 patients’ concomitant medications (see Tables 1-3 or Table 5); reduced maintenance doses may

154 be effective for patients with significant renal impairment [*see Use in Specific Populations (8.7),*  
155 *Clinical Pharmacology (12.3)*]. Few patients with severe renal impairment have been evaluated  
156 during chronic treatment with LAMICTAL. Because there is inadequate experience in this  
157 population, LAMICTAL should be used with caution in these patients.

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

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

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

167 **Bipolar Disorder:** In the controlled clinical trials, there was no increase in the  
168 incidence, type, or severity of adverse reactions following abrupt termination of LAMICTAL. In  
169 clinical trials in patients with Bipolar Disorder, 2 patients experienced seizures shortly after  
170 abrupt withdrawal of LAMICTAL. However, there were confounding factors that may have  
171 contributed to the occurrence of seizures in these bipolar patients. Discontinuation of  
172 LAMICTAL should involve a step-wise reduction of dose over at least 2 weeks (approximately  
173 50% per week) unless safety concerns require a more rapid withdrawal [*see Warnings and*  
174 *Precautions (5.9)*].

## 175 **2.2 Epilepsy – Adjunctive Therapy**

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

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

184

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

	For Patients TAKING Valproate <sup>a</sup>	For Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone, <sup>b</sup> or Valproate <sup>a</sup>	For Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone <sup>b</sup> and NOT TAKING Valproate <sup>a</sup>
Weeks 1 and 2	<b>25 mg every other day</b>	<b>25 mg every day</b>	<b>50 mg/day</b>
Weeks 3 and 4	<b>25 mg every day</b>	<b>50 mg/day</b>	<b>100 mg/day</b> (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	<b>100 to 200 mg/day with valproate alone</b>  <b>100 to 400 mg/day with valproate and other drugs that induce glucuronidation</b>  (in 1 or 2 divided doses)	<b>225 to 375 mg/day</b> (in 2 divided doses)	<b>300 to 500 mg/day</b> (in 2 divided doses)

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

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

196  
 197 Patients 2 to 12 Years of Age: Recommended dosing guidelines are summarized in  
 198 Table 2.

199 Smaller starting doses and slower dose escalations than those used in clinical trials are  
 200 recommended because of the suggestion that the risk of rash may be decreased by smaller  
 201 starting doses and slower dose escalations. Therefore, maintenance doses will take longer to  
 202 reach in clinical practice than in clinical trials. It may take several weeks to months to achieve an

203 individualized maintenance dose. Maintenance doses in patients weighing less than 30 kg,  
 204 regardless of age or concomitant AED, may need to be increased as much as 50%, based on  
 205 clinical response.

206 **The smallest available strength of LAMICTAL Chewable Dispersible Tablets is 2**  
 207 **mg, and only whole tablets should be administered. If the calculated dose cannot be**  
 208 **achieved using whole tablets, the dose should be rounded down to the nearest whole tablet**  
 209 *[see How Supplied/Storage and Handling (16) and Medication Guide].*  
 210

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

	For Patients TAKING Valproate <sup>a</sup>	For Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone, <sup>b</sup> or Valproate <sup>a</sup>	For Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone <sup>b</sup> and NOT TAKING Valproate <sup>a</sup>
Weeks 1 and 2	<b>0.15 mg/kg/day</b> in 1 or 2 divided doses, rounded down to the nearest whole tablet (see Table 3 for weight-based dosing guide)	<b>0.3 mg/kg/day</b> in 1 or 2 divided doses, rounded down to the nearest whole tablet	<b>0.6 mg/kg/day</b> in 2 divided doses, rounded down to the nearest whole tablet
Weeks 3 and 4	<b>0.3 mg/kg/day</b> in 1 or 2 divided doses, rounded down to the nearest whole tablet (see Table 3 for weight-based dosing guide)	<b>0.6 mg/kg/day</b> in 2 divided doses, rounded down to the nearest whole tablet	<b>1.2 mg/kg/day</b> 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 administered daily dose	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

Usual maintenance dose	<b>1 to 5 mg/kg/day</b> (maximum 200 mg/day in 1 or 2 divided doses)  <b>1 to 3 mg/kg/day</b> with valproate alone	<b>4.5 to 7.5 mg/kg/day</b> (maximum 300 mg/day in 2 divided doses)	<b>5 to 15 mg/kg/day</b> (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

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

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

216 <sup>b</sup> These drugs induce lamotrigine glucuronidation and increase clearance [see *Drug Interactions*  
 217 *(7), Clinical Pharmacology (12.3)*]. Other drugs that have similar effects include estrogen-  
 218 containing oral contraceptives [see *Drug Interactions (7), Clinical Pharmacology (12.3)*].  
 219 Dosing recommendations for oral contraceptives can be found in General Dosing  
 220 Considerations [see *Dosage and Administration (2.1)*]. Patients on rifampin, or other drugs  
 221 that induce lamotrigine glucuronidation and increase clearance, should follow the same dosing  
 222 titration/maintenance regimen as that used with anticonvulsants that have this effect.  
 223

224 **Table 3. The Initial Weight-Based Dosing Guide for Patients 2 to 12 Years of Age Taking**  
 225 **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 <i>other</i> 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

226  
 227 **Usual Adjunctive Maintenance Dose for Epilepsy:** The usual maintenance doses  
 228 identified in Tables 1 and 2 are derived from dosing regimens employed in the placebo-  
 229 controlled adjunctive studies in which the efficacy of LAMICTAL was established. In patients  
 230 receiving multidrug regimens employing carbamazepine, phenytoin, phenobarbital, or primidone  
 231 **without valproate**, maintenance doses of adjunctive LAMICTAL as high as 700 mg/day have  
 232 been used. In patients receiving **valproate alone**, maintenance doses of adjunctive LAMICTAL  
 233 as high as 200 mg/day have been used. The advantage of using doses above those recommended  
 234 in Tables 1 through 4 has not been established in controlled trials.

235 **2.3 Epilepsy – Conversion From Adjunctive Therapy to Monotherapy**

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

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

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

243 Conversion From Adjunctive Therapy With Carbamazepine, Phenytoin,  
244 Phenobarbital, or Primidone to Monotherapy With LAMICTAL: After achieving a dose of  
245 500 mg/day of LAMICTAL according to the guidelines in Table 1, the concomitant AED should  
246 be withdrawn by 20% decrements each week over a 4-week period. The regimen for the  
247 withdrawal of the concomitant AED is based on experience gained in the controlled  
248 monotherapy clinical trial.

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

251

252 **Table 4. Conversion From Adjunctive Therapy With Valproate to Monotherapy With**  
253 **LAMICTAL in Patients  $\geq 16$  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.

254

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

## 260 **2.4 Bipolar Disorder**

261 The goal of maintenance treatment with LAMICTAL is to delay the time to occurrence of  
262 mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute

263 mood episodes with standard therapy. The target dose of LAMICTAL is 200 mg/day (100  
 264 mg/day in patients taking valproate, which decreases the apparent clearance of lamotrigine, and  
 265 400 mg/day in patients not taking valproate and taking either carbamazepine, phenytoin,  
 266 phenobarbital, primidone, or other drugs such as rifampin that increase the apparent clearance of  
 267 lamotrigine). In the clinical trials, doses up to 400 mg/day as monotherapy were evaluated;  
 268 however, no additional benefit was seen at 400 mg/day compared with 200 mg/day [see *Clinical*  
 269 *Studies (14.2)*]. Accordingly, doses above 200 mg/day are not recommended. Treatment with  
 270 LAMICTAL is introduced, based on concurrent medications, according to the regimen outlined  
 271 in Table 5. If other psychotropic medications are withdrawn following stabilization, the dose of  
 272 LAMICTAL should be adjusted. For patients discontinuing valproate, the dose of LAMICTAL  
 273 should be doubled over a 2-week period in equal weekly increments (see Table 6). For patients  
 274 discontinuing carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as  
 275 rifampin that induce lamotrigine glucuronidation, the dose of LAMICTAL should remain  
 276 constant for the first week and then should be decreased by half over a 2-week period in equal  
 277 weekly decrements (see Table 6). The dose of LAMICTAL may then be further adjusted to the  
 278 target dose (200 mg) as clinically indicated.

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

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

284

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

	For Patients TAKING Valproate <sup>a</sup>	For Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone, <sup>b</sup> or Valproate <sup>a</sup>	For Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone <sup>b</sup> and NOT TAKING Valproate <sup>a</sup>
Weeks 1 and 2	25 mg every <i>other</i> 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

286 <sup>a</sup> Valproate has been shown to inhibit glucuronidation and decrease the apparent clearance of  
 287 lamotrigine [see *Drug Interactions (7), Clinical Pharmacology (12.3)*].  
 288 <sup>b</sup> These drugs induce lamotrigine glucuronidation and increase clearance [see *Drug Interactions*  
 289 *(7), Clinical Pharmacology (12.3)*]. Other drugs that have similar effects include estrogen-  
 290 containing oral contraceptives [see *Drug Interactions (7), Clinical Pharmacology (12.3)*].  
 291 Dosing recommendations for oral contraceptives can be found in General Dosing  
 292 Considerations [see *Dosage and Administration (2.1)*]. Patients on rifampin, or other drugs  
 293 that induce lamotrigine glucuronidation and increase clearance, should follow the same dosing  
 294 titration/maintenance regimen as that used with anticonvulsants that have this effect.  
 295

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

	Discontinuation of Psychotropic Drugs (excluding Carbamazepine, Phenytoin, Phenobarbital, Primidone, <sup>b</sup> or Valproate <sup>a</sup> )	After Discontinuation of Valproate <sup>a</sup>	After Discontinuation of Carbamazepine, Phenytoin, Phenobarbital, or Primidone <sup>b</sup>
		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

298 <sup>a</sup> Valproate has been shown to inhibit glucuronidation and decrease the apparent clearance of  
 299 lamotrigine [see *Drug Interactions (7), Clinical Pharmacology (12.3)*].  
 300 <sup>b</sup> These drugs induce lamotrigine glucuronidation and increase clearance [see *Drug Interactions*  
 301 *(7), Clinical Pharmacology (12.3)*]. Other drugs that have similar effects include estrogen-  
 302 containing oral contraceptives [see *Drug Interactions (7), Clinical Pharmacology (12.3)*].  
 303 Dosing recommendations for oral contraceptives can be found in General Dosing  
 304 Considerations [see *Dosage and Administration (2.1)*]. Patients on rifampin, or other drugs  
 305 that induce lamotrigine glucuronidation and increase clearance, should follow the same dosing  
 306 titration/maintenance regimen as that used with anticonvulsants that have this effect.  
 307

308 The benefit of continuing treatment in patients who had been stabilized in an 8- to 16-  
 309 week open-label phase with LAMICTAL was established in 2 randomized, placebo-controlled  
 310 clinical maintenance trials [see *Clinical Studies (14.2)*]. However, the optimal duration of

311 treatment with LAMICTAL has not been established. Thus, patients should be periodically  
312 reassessed to determine the need for maintenance treatment.

### 313 **2.5 Administration of LAMICTAL Chewable Dispersible Tablets**

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

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

### 321 **2.6 Administration of LAMICTAL ODT Orally Disintegrating Tablets**

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

## 325 **3 DOSAGE FORMS AND STRENGTHS**

### 326 **3.1 Tablets**

327 25 mg, white, scored, shield-shaped tablets debossed with “LAMICTAL” and “25.”  
328 100 mg, peach, scored, shield-shaped tablets debossed with “LAMICTAL” and “100.”  
329 150 mg, cream, scored, shield-shaped tablets debossed with “LAMICTAL” and “150.”  
330 200 mg, blue, scored, shield-shaped tablets debossed with “LAMICTAL” and “200.”

### 331 **3.2 Chewable Dispersible Tablets**

332 2 mg, white to off-white, round tablets debossed with “LTG” over “2.”  
333 5 mg, white to off-white, caplet-shaped tablets debossed with “GX CL2.”  
334 25 mg, white, super elliptical-shaped tablets debossed with “GX CL5.”

### 335 **3.3 Orally Disintegrating Tablets**

336 25 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with “LMT”  
337 on one side and “25” on the other side.

338 50 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with “LMT”  
339 on one side and “50” on the other side.

340 100 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with  
341 “LAMICTAL” on one side and “100” on the other side.

342 200 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with  
343 “LAMICTAL” on one side and “200” on the other side.

### 344 **3.4 Potential Medication Errors**

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

349 **4 CONTRAINDICATIONS**

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

352 **5 WARNINGS AND PRECAUTIONS**

353 **5.1 Serious Skin Rashes [*see Boxed Warning*]**

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

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

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

375 Among the rashes leading to hospitalization were Stevens-Johnson syndrome, toxic  
376 epidermal necrolysis, angioedema, and those associated with multiorgan hypersensitivity [*see*  
377 *Warnings and Precautions (5.2)*].

378 There is evidence that the inclusion of valproate in a multidrug regimen increases the risk  
379 of serious, potentially life-threatening rash in adults. Specifically, of 584 patients administered  
380 LAMICTAL with valproate in epilepsy clinical trials, 6 (1%) were hospitalized in association  
381 with rash; in contrast, 4 (0.16%) of 2,398 clinical trial patients and volunteers administered  
382 LAMICTAL in the absence of valproate were hospitalized.

383 Patients With History of Allergy or Rash to Other Antiepileptic Drugs: The risk of  
384 nonserious rash may be increased when the recommended initial dose and/or the rate of dose  
385 escalation of LAMICTAL is exceeded and in patients with a history of allergy or rash to other  
386 AEDs.

387 **5.2 Multiorgan Hypersensitivity Reactions and Organ Failure**

388 Multiorgan hypersensitivity reactions, also known as Drug Reaction with Eosinophilia  
389 and Systemic Symptoms (DRESS), have occurred with LAMICTAL. Some have been fatal or  
390 life threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or  
391 lymphadenopathy in association with other organ system involvement, such as hepatitis,  
392 nephritis, hematologic abnormalities, myocarditis, or myositis, sometimes resembling an acute  
393 viral infection. Eosinophilia is often present. This disorder is variable in its expression, and other  
394 organ systems not noted here may be involved.

395 Fatalities associated with acute multiorgan failure and various degrees of hepatic failure  
396 have been reported in 2 of 3,796 adult patients and 4 of 2,435 pediatric patients who received  
397 LAMICTAL in epilepsy clinical trials. Rare fatalities from multiorgan failure have also been  
398 reported in postmarketing use.

399 Isolated liver failure without rash or involvement of other organs has also been reported  
400 with LAMICTAL.

401 It is important to note that early manifestations of hypersensitivity (e.g., fever,  
402 lymphadenopathy) may be present even though a rash is not evident. If such signs or symptoms  
403 are present, the patient should be evaluated immediately. LAMICTAL should be discontinued if  
404 an alternative etiology for the signs or symptoms cannot be established.

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

### 409 **5.3 Blood Dyscrasias**

410 There have been reports of blood dyscrasias that may or may not be associated with  
411 multiorgan hypersensitivity (also known as DRESS) [*see Warnings and Precautions (5.2)*].  
412 These have included neutropenia, leukopenia, anemia, thrombocytopenia, pancytopenia, and,  
413 rarely, aplastic anemia and pure red cell aplasia.

### 414 **5.4 Suicidal Behavior and Ideation**

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

419 Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy)  
420 of 11 different AEDs showed that patients randomized to one of the AEDs had approximately  
421 twice the risk (adjusted Relative Risk 1.8, 95% CI: 1.2, 2.7) of suicidal thinking or behavior  
422 compared to patients randomized to placebo. In these trials, which had a median treatment  
423 duration of 12 weeks, the estimated incidence of suicidal behavior or ideation among 27,863  
424 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients,  
425 representing an increase of approximately 1 case of suicidal thinking or behavior for every 530  
426 patients treated. There were 4 suicides in drug-treated patients in the trials and none in placebo-

427 treated patients, but the number of events is too small to allow any conclusion about drug effect  
428 on suicide.

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

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

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

438

439 **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

440

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

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

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

455 **5.5 Use in Patients With Bipolar Disorder**

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

458 Children and Adolescents (less than 18 years of age): Safety and effectiveness of  
459 LAMICTAL in patients below the age of 18 years with mood disorders have not been  
460 established [*see Suicidal Behavior and Ideation (5.4)*].

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

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

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

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

## 479 **5.6 Aseptic Meningitis**

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

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

493 Cerebrospinal fluid (CSF) analyzed at the time of clinical presentation in reported cases  
494 was characterized by a mild to moderate pleocytosis, normal glucose levels, and mild to

495 moderate increase in protein. CSF white blood cell count differentials showed a predominance of  
496 neutrophils in a majority of the cases, although a predominance of lymphocytes was reported in  
497 approximately one third of the cases. Some patients also had new onset of signs and symptoms  
498 of involvement of other organs (predominantly hepatic and renal involvement), which may  
499 suggest that in these cases the aseptic meningitis observed was part of a hypersensitivity reaction  
500 [see *Warnings and Precautions (5.2)*].

### 501 **5.7 Potential Medication Errors**

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

### 513 **5.8 Concomitant Use With Oral Contraceptives**

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

### 521 **5.9 Withdrawal Seizures**

522 As with other AEDs, LAMICTAL should not be abruptly discontinued. In patients with  
523 epilepsy there is a possibility of increasing seizure frequency. In clinical trials in patients with  
524 Bipolar Disorder, 2 patients experienced seizures shortly after abrupt withdrawal of  
525 LAMICTAL; however, there were confounding factors that may have contributed to the  
526 occurrence of seizures in these bipolar patients. Unless safety concerns require a more rapid  
527 withdrawal, the dose of LAMICTAL should be tapered over a period of at least 2 weeks  
528 (approximately 50% reduction per week) [see *Dosage and Administration (2.1)*].

### 529 **5.10 Status Epilepticus**

530 Valid estimates of the incidence of treatment-emergent status epilepticus among patients  
531 treated with LAMICTAL are difficult to obtain because reporters participating in clinical trials  
532 did not all employ identical rules for identifying cases. At a minimum, 7 of 2,343 adult patients  
533 had episodes that could unequivocally be described as status epilepticus. In addition, a number of

534 reports of variably defined episodes of seizure exacerbation (e.g., seizure clusters, seizure  
535 flurries) were made.

### 536 **5.11 Sudden Unexplained Death in Epilepsy (SUDEP)**

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

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

### 554 **5.12 Addition of LAMICTAL to a Multidrug Regimen That Includes Valproate**

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

### 557 **5.13 Binding in the Eye and Other Melanin-Containing Tissues**

558 Because lamotrigine binds to melanin, it could accumulate in melanin-rich tissues over  
559 time. This raises the possibility that lamotrigine may cause toxicity in these tissues after  
560 extended use. Although ophthalmological testing was performed in one controlled clinical trial,  
561 the testing was inadequate to exclude subtle effects or injury occurring after long-term exposure.  
562 Moreover, the capacity of available tests to detect potentially adverse consequences, if any, of  
563 lamotrigine's binding to melanin is unknown [*see Clinical Pharmacology (12.2)*].

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

### 567 **5.14 Laboratory Tests**

568 The value of monitoring plasma concentrations of lamotrigine in patients treated with  
569 LAMICTAL has not been established. Because of the possible pharmacokinetic interactions  
570 between lamotrigine and other drugs including AEDs (see Table 15), monitoring of the plasma  
571 levels of lamotrigine and concomitant drugs may be indicated, particularly during dosage

572 adjustments. In general, clinical judgment should be exercised regarding monitoring of plasma  
573 levels of lamotrigine and other drugs and whether or not dosage adjustments are necessary.

## 574 **6 ADVERSE REACTIONS**

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

- 577 • Serious skin rashes [*see Warnings and Precautions (5.1)*]
- 578 • Multiorgan hypersensitivity reactions and organ failure [*see Warnings and Precautions (5.2)*]
- 579 • Blood dyscrasias [*see Warnings and Precautions (5.3)*]
- 580 • Suicidal behavior and ideation [*see Warnings and Precautions (5.4)*]
- 581 • Aseptic meningitis [*see Warnings and Precautions (5.6)*]
- 582 • Withdrawal seizures [*see Warnings and Precautions (5.9)*]
- 583 • Status epilepticus [*see Warnings and Precautions (5.10)*]
- 584 • Sudden unexplained death in epilepsy [*see Warnings and Precautions (5.11)*]

### 585 **6.1 Clinical Trials**

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

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

593 Epilepsy: Most Common Adverse Reactions in All Clinical Studies: Adjunctive  
594 Therapy in Adults With Epilepsy: The most commonly observed ( $\geq 5\%$  for LAMICTAL and  
595 more common on drug than placebo) adverse reactions seen in association with LAMICTAL  
596 during adjunctive therapy in adults and not seen at an equivalent frequency among placebo-  
597 treated patients were: dizziness, ataxia, somnolence, headache, diplopia, blurred vision, nausea,  
598 vomiting, and rash. Dizziness, diplopia, ataxia, blurred vision, nausea, and vomiting were dose-  
599 related. Dizziness, diplopia, ataxia, and blurred vision occurred more commonly in patients  
600 receiving carbamazepine with LAMICTAL than in patients receiving other AEDs with  
601 LAMICTAL. Clinical data suggest a higher incidence of rash, including serious rash, in patients  
602 receiving concomitant valproate than in patients not receiving valproate [*see Warnings and*  
603 *Precautions (5.1)*].

604 Approximately 11% of the 3,378 adult patients who received LAMICTAL as adjunctive  
605 therapy in premarketing clinical trials discontinued treatment because of an adverse reaction. The  
606 adverse reactions most commonly associated with discontinuation were rash (3.0%), dizziness  
607 (2.8%), and headache (2.5%).

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

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

621 Approximately 10% of the 420 adult patients who received LAMICTAL as monotherapy  
622 in premarketing clinical trials discontinued treatment because of an adverse reaction. The  
623 adverse reactions most commonly associated with discontinuation were rash (4.5%), headache  
624 (3.1%), and asthenia (2.4%).

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

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

635 Approximately 11.5% of the 1,081 pediatric patients 2 to 16 years of age who received  
636 LAMICTAL as adjunctive therapy in premarketing clinical trials discontinued treatment because  
637 of an adverse reaction. The adverse reactions most commonly associated with discontinuation  
638 were rash (4.4%), reaction aggravated (1.7%), and ataxia (0.6%).

639 **Controlled Adjunctive Clinical Studies in Adults With Epilepsy:** Table 8 lists  
640 treatment-emergent adverse reactions that occurred in at least 2% of adult patients with epilepsy  
641 treated with LAMICTAL in placebo-controlled trials and were numerically more common in the  
642 patients treated with LAMICTAL. In these studies, either LAMICTAL or placebo was added to  
643 the patient's current AED therapy. Adverse reactions were usually mild to moderate in intensity.  
644

645 **Table 8. Treatment-Emergent Adverse Reaction Incidence in Placebo-Controlled**  
 646 **Adjunctive Trials in Adult Patients With Epilepsy<sup>a</sup> (Adverse reactions in at least 2% of**  
 647 **patients treated with LAMICTAL and numerically more frequent than in the placebo**  
 648 **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

649 <sup>a</sup> Patients in these adjunctive studies were receiving 1 to 3 of the following concomitant AEDs  
 650 (carbamazepine, phenytoin, phenobarbital, or primidone) in addition to LAMICTAL or  
 651 placebo. Patients may have reported multiple adverse reactions during the study or at  
 652 discontinuation; thus, patients may be included in more than one category.  
 653

654 In a randomized, parallel study comparing placebo and 300 and 500 mg/day of  
 655 LAMICTAL, some of the more common drug-related adverse reactions were dose-related (see  
 656 Table 9).  
 657

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

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

660 <sup>a</sup> Significantly greater than placebo group ( $P < 0.05$ ).

661 <sup>b</sup> Significantly greater than group receiving LAMICTAL 300 mg ( $P < 0.05$ ).

662

663 The overall adverse reaction profile for LAMICTAL was similar between females and  
 664 males, and was independent of age. Because the largest non-Caucasian racial subgroup was only  
 665 6% of patients exposed to LAMICTAL in placebo-controlled trials, there are insufficient data to  
 666 support a statement regarding the distribution of adverse reaction reports by race. Generally,  
 667 females receiving either LAMICTAL as adjunctive therapy or placebo were more likely to report  
 668 adverse reactions than males. The only adverse reaction for which the reports on LAMICTAL  
 669 were greater than 10% more frequent in females than males (without a corresponding difference  
 670 by gender on placebo) was dizziness (difference = 16.5%). There was little difference between  
 671 females and males in the rates of discontinuation of LAMICTAL for individual adverse  
 672 reactions.

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

678

679 **Table 10. Treatment-Emergent Adverse Reaction Incidence in Adults With Partial**  
 680 **Seizures in a Controlled Monotherapy Trial<sup>a</sup> (Adverse reactions in at least 5% of**  
 681 **patients treated with LAMICTAL and numerically more frequent than in the valproate**  
 682 **group.)**

Body System/ Adverse Reaction	Percent of Patients Receiving LAMICTAL as Monotherapy <sup>b</sup> (n = 43)	Percent of Patients Receiving Low-Dose Valproate <sup>c</sup> 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

683 <sup>a</sup> Patients in these studies were converted to LAMICTAL or valproate monotherapy from  
 684 adjunctive therapy with carbamazepine or phenytoin. Patients may have reported multiple  
 685 adverse reactions during the study; thus, patients may be included in more than one category.

686 <sup>b</sup> Up to 500 mg/day.

687 <sup>c</sup> 1,000 mg/day.

688

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

691 *Body as a Whole:* Asthenia, fever.

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

693 *Metabolic and Nutritional:* Peripheral edema.

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

696 *Respiratory:* Epistaxis, bronchitis, dyspnea.

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

698 *Special Senses:* Vision abnormality.

699

700 *Incidence in Controlled Adjunctive Trials in Pediatric Patients With*  
 701 *Epilepsy:* Table 11 lists adverse reactions that occurred in at least 2% of 339 pediatric patients  
 702 with partial seizures or generalized seizures of Lennox-Gastaut syndrome, who received  
 703 LAMICTAL up to 15 mg/kg/day or a maximum of 750 mg/day. Reported adverse reactions were  
 704 classified using COSTART terminology.

705 **Table 11. Treatment-Emergent Adverse Reaction Incidence in Placebo-Controlled**  
 706 **Adjunctive Trials in Pediatric Patients With Epilepsy (Adverse reactions in at least 2%**  
 707 **of patients treated with LAMICTAL and numerically more frequent than in the placebo**  
 708 **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

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**Bipolar Disorder:** The most commonly observed ( $\geq 5\%$ ) treatment-emergent adverse reactions seen in association with the use of LAMICTAL as monotherapy (100 to 400 mg/day) in adult patients ( $\geq 18$  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%).

719 During the monotherapy phase of the double-blind, placebo-controlled trials of 18  
 720 months' duration, 13% of 227 patients who received LAMICTAL (100 to 400 mg/day), 16% of  
 721 190 patients who received placebo, and 23% of 166 patients who received lithium discontinued  
 722 therapy because of an adverse reaction. The adverse reactions which most commonly led to  
 723 discontinuation of LAMICTAL were rash (3%) and mania/hypomania/mixed mood adverse  
 724 reactions (2%). Approximately 16% of 2,401 patients who received LAMICTAL (50 to  
 725 500 mg/day) for Bipolar Disorder in premarketing trials discontinued therapy because of an  
 726 adverse reaction, most commonly due to rash (5%) and mania/hypomania/mixed mood adverse  
 727 reactions (2%).

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

730

731 **Table 12. Treatment-Emergent Adverse Reaction Incidence in 2 Placebo-Controlled**  
 732 **Trials in Adults With Bipolar I Disorder<sup>a</sup> (Adverse reactions in at least 5% of patients**  
 733 **treated with LAMICTAL as monotherapy and numerically more frequent than in the**  
 734 **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) <sup>b</sup>	7	5

735 <sup>a</sup> Patients in these studies were converted to LAMICTAL (100 to 400 mg/day) or placebo  
 736 monotherapy from add-on therapy with other psychotropic medications. Patients may have

737 reported multiple adverse reactions during the study; thus, patients may be included in  
738 more than one category.

739 <sup>b</sup> In the overall bipolar and other mood disorders clinical trials, the rate of serious rash was  
740 0.08% (1 of 1,233) of adult patients who received LAMICTAL as initial monotherapy and  
741 0.13% (2 of 1,538) of adult patients who received LAMICTAL as adjunctive therapy [*see*  
742 *Warnings and Precautions (5.1)*].  
743

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

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

749 *General:* Fever, neck pain.

750 *Cardiovascular:* Migraine.

751 *Digestive:* Flatulence.

752 *Metabolic and Nutritional:* Weight gain, edema.

753 *Musculoskeletal:* Arthralgia, myalgia.

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

756 *Respiratory:* Sinusitis.

757 *Urogenital:* Urinary frequency.

758 *Adverse Reactions Following Abrupt Discontinuation:* In the 2 maintenance trials,  
759 there was no increase in the incidence, severity, or type of adverse reactions in Bipolar Disorder  
760 patients after abruptly terminating therapy with LAMICTAL. In clinical trials in patients with  
761 Bipolar Disorder, 2 patients experienced seizures shortly after abrupt withdrawal of  
762 LAMICTAL. However, there were confounding factors that may have contributed to the  
763 occurrence of seizures in these bipolar patients [*see Warnings and Precautions (5.9)*].

764 *Mania/Hypomania/Mixed Episodes:* During the double-blind, placebo-controlled  
765 clinical trials in Bipolar I Disorder in which patients were converted to monotherapy with  
766 LAMICTAL (100 to 400 mg/day) from other psychotropic medications and followed for up to  
767 18 months, the rates of manic or hypomanic or mixed mood episodes reported as adverse  
768 reactions were 5% for patients treated with LAMICTAL (n = 227), 4% for patients treated with  
769 lithium (n = 166), and 7% for patients treated with placebo (n = 190). In all bipolar controlled  
770 trials combined, adverse reactions of mania (including hypomania and mixed mood episodes)  
771 were reported in 5% of patients treated with LAMICTAL (n = 956), 3% of patients treated with  
772 lithium (n = 280), and 4% of patients treated with placebo (n = 803).

## 773 **6.2 Other Adverse Reactions Observed in All Clinical Trials**

774 LAMICTAL has been administered to 6,694 individuals for whom complete adverse  
775 reaction data was captured during all clinical trials, only some of which were placebo controlled.

776 During these trials, all adverse reactions were recorded by the clinical investigators using  
777 terminology of their own choosing. To provide a meaningful estimate of the proportion of  
778 individuals having adverse reactions, similar types of adverse reactions were grouped into a  
779 smaller number of standardized categories using modified COSTART dictionary terminology.  
780 The frequencies presented represent the proportion of the 6,694 individuals exposed to  
781 LAMICTAL who experienced an event of the type cited on at least one occasion while receiving  
782 LAMICTAL. All reported adverse reactions are included except those already listed in the  
783 previous tables or elsewhere in the labeling, those too general to be informative, and those not  
784 reasonably associated with the use of the drug.

785 Adverse reactions are further classified within body system categories and enumerated in  
786 order of decreasing frequency using the following definitions: *frequent* adverse reactions are  
787 defined as those occurring in at least 1/100 patients; *infrequent* adverse reactions are those  
788 occurring in 1/100 to 1/1,000 patients; *rare* adverse reactions are those occurring in fewer than  
789 1/1,000 patients.

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

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

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

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

801 Endocrine System: *Rare:* Goiter and hypothyroidism.

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

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

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

810 Nervous System: *Frequent:* Confusion and paresthesia. *Infrequent:* Akathisia, apathy,  
811 aphasia, central nervous system (CNS) depression, depersonalization, dysarthria, dyskinesia,  
812 euphoria, hallucinations, hostility, hyperkinesia, hypertonia, libido decreased, memory decrease,  
813 mind racing, movement disorder, myoclonus, panic attack, paranoid reaction, personality  
814 disorder, psychosis, sleep disorder, stupor, and suicidal ideation. *Rare:* Choreoathetosis,

815 delirium, delusions, dysphoria, dystonia, extrapyramidal syndrome, faintness, grand mal  
 816 convulsions, hemiplegia, hyperalgesia, hyperesthesia, hypokinesia, hypotonia, manic depression  
 817 reaction, muscle spasm, neuralgia, neurosis, paralysis, and peripheral neuritis.

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

819 Special Senses: *Frequent:* Amblyopia. *Infrequent:* Abnormality of accommodation,  
 820 conjunctivitis, dry eyes, ear pain, photophobia, taste perversion, and tinnitus. *Rare:* Deafness,  
 821 lacrimation disorder, oscillopsia, parosmia, ptosis, strabismus, taste loss, uveitis, and visual field  
 822 defect.

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

827 **6.3 Postmarketing Experience**

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

832 Blood and Lymphatic: Agranulocytosis, hemolytic anemia, lymphadenopathy not  
 833 associated with hypersensitivity disorder.

834 Gastrointestinal: Esophagitis.

835 Hepatobiliary Tract and Pancreas: Pancreatitis.

836 Immunologic: Lupus-like reaction, vasculitis.

837 Lower Respiratory: Apnea.

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

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

842 Non-site Specific: Progressive immunosuppression.

843 **7 DRUG INTERACTIONS**

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

847

848 **Table 13. Established and Other Potentially Significant Drug Interactions**

Concomitant Drug	Effect on Concentration of Lamotrigine or Concomitant Drug	Clinical Comment
Estrogen-containing oral	↓ lamotrigine	Decreased lamotrigine levels

contraceptive preparations containing 30 mcg ethinylestradiol and 150 mcg levonorgestrel	↓ levonorgestrel	approximately 50%. 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.

849 ↓ = Decreased (induces lamotrigine glucuronidation).

850 ↑ = Increased (inhibits lamotrigine glucuronidation).

851 ? = Conflicting data.

## 852 **8 USE IN SPECIFIC POPULATIONS**

### 853 **8.1 Pregnancy**

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

863 A behavioral teratology study was conducted in rats dosed during the period of  
 864 organogenesis. At day 21 postpartum, offspring of dams receiving 5 mg/kg/day or higher

865 displayed a significantly longer latent period for open field exploration and a lower frequency of  
866 rearing. In a swimming maze test performed on days 39 to 44 postpartum, time to completion  
867 was increased in offspring of dams receiving 25 mg/kg/day. These doses represent 0.1 and 0.5  
868 times the clinical dose on a mg/m<sup>2</sup> basis, respectively.

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

872 When pregnant rats were orally dosed at 0.1, 0.14, or 0.3 times the highest human  
873 maintenance dose (on a mg/m<sup>2</sup> basis) during the latter part of gestation (days 15 to 20), maternal  
874 toxicity and fetal death were seen. In dams, food consumption and weight gain were reduced,  
875 and the gestation period was slightly prolonged (22.6 vs. 22.0 days in the control group).  
876 Stillborn pups were found in all 3 drug-treated groups with the highest number in the high-dose  
877 group. Postnatal death was also seen, but only in the 2 highest doses, and occurred between days  
878 1 and 20. Some of these deaths appear to be drug-related and not secondary to the maternal  
879 toxicity. A no-observed-effect level (NOEL) could not be determined for this study.

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

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

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

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

## 901 **8.2 Labor and Delivery**

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

## 903 **8.3 Nursing Mothers**

904 Lamotrigine is present in milk from lactating women taking LAMICTAL. Data from  
905 multiple small studies indicate that lamotrigine plasma levels in human milk-fed infants have  
906 been reported to be as high as 50% of the maternal serum levels. Neonates and young infants are  
907 at risk for high serum levels because maternal serum and milk levels can rise to high levels  
908 postpartum if lamotrigine dosage has been increased during pregnancy but not later reduced to  
909 the pre-pregnancy dosage. Lamotrigine exposure is further increased due to the immaturity of the  
910 infant glucuronidation capacity needed for drug clearance. Events including apnea, drowsiness,  
911 and poor sucking have been reported in infants who have been human milk-fed by mothers using  
912 lamotrigine; whether or not these events were caused by lamotrigine is unknown. Human  
913 milk-fed infants should be closely monitored for adverse events resulting from lamotrigine.  
914 Measurement of infant serum levels should be performed to rule out toxicity if concerns arise.  
915 Human milk-feeding should be discontinued in infants with lamotrigine toxicity. Caution should  
916 be exercised when LAMICTAL is administered to a nursing woman.

#### 917 **8.4 Pediatric Use**

918 LAMICTAL is indicated for adjunctive therapy in patients  $\geq 2$  years of age for partial  
919 seizures, the generalized seizures of Lennox-Gastaut syndrome, and primary generalized tonic-  
920 clonic seizures.

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

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

#### 931 **8.5 Geriatric Use**

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

#### 938 **8.6 Patients With Hepatic Impairment**

939 Experience in patients with hepatic impairment is limited. Based on a clinical  
940 pharmacology study in 24 patients with mild, moderate, and severe liver impairment [*see*  
941 *Clinical Pharmacology (12.3)*], the following general recommendations can be made. No dosage  
942 adjustment is needed in patients with mild liver impairment. Initial, escalation, and maintenance

943 doses should generally be reduced by approximately 25% in patients with moderate and severe  
944 liver impairment without ascites and 50% in patients with severe liver impairment with ascites.  
945 Escalation and maintenance doses may be adjusted according to clinical response [*see Dosage*  
946 *and Administration (2.1)*].

## 947 **8.7 Patients With Renal Impairment**

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

953 Initial doses of LAMICTAL should be based on patients' AED regimens; reduced  
954 maintenance doses may be effective for patients with significant renal impairment. Few patients  
955 with severe renal impairment have been evaluated during chronic treatment with LAMICTAL.  
956 Because there is inadequate experience in this population, LAMICTAL should be used with  
957 caution in these patients [*see Dosage and Administration (2.1)*].

## 958 **10 OVERDOSAGE**

### 959 **10.1 Human Overdose Experience**

960 Overdoses involving quantities up to 15 g have been reported for LAMICTAL, some of  
961 which have been fatal. Overdose has resulted in ataxia, nystagmus, seizures (including tonic-  
962 clonic seizures), decreased level of consciousness, coma, and intraventricular conduction delay.

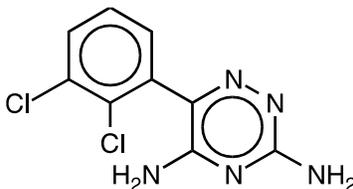
### 963 **10.2 Management of Overdose**

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

## 973 **11 DESCRIPTION**

974 LAMICTAL (lamotrigine), an AED of the phenyltriazine class, is chemically unrelated to  
975 existing AEDs. Its chemical name is 3,5-diamino-6-(2,3-dichlorophenyl)-*as*-triazine, its  
976 molecular formula is C<sub>9</sub>H<sub>7</sub>N<sub>5</sub>Cl<sub>2</sub>, and its molecular weight is 256.09. Lamotrigine is a white to  
977 pale cream-colored powder and has a pK<sub>a</sub> of 5.7. Lamotrigine is very slightly soluble in water  
978 (0.17 mg/mL at 25°C) and slightly soluble in 0.1 M HCl (4.1 mg/mL at 25°C). The structural  
979 formula is:

980



981  
982

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

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

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

998 LAMICTAL ODT Orally Disintegrating Tablets are formulated using technologies  
999 (Microcaps<sup>®</sup> and AdvaTab<sup>®</sup>) designed to mask the bitter taste of lamotrigine and achieve a rapid  
1000 dissolution profile. Tablet characteristics including flavor, mouth-feel, after-taste, and ease of use  
1001 were rated as favorable in a study of 108 healthy volunteers.

## 1002 **12 CLINICAL PHARMACOLOGY**

### 1003 **12.1 Mechanism of Action**

1004 The precise mechanism(s) by which lamotrigine exerts its anticonvulsant action are  
1005 unknown. In animal models designed to detect anticonvulsant activity, lamotrigine was effective  
1006 in preventing seizure spread in the maximum electroshock (MES) and pentylenetetrazol (scMet)  
1007 tests, and prevented seizures in the visually and electrically evoked after-discharge (EEAD) tests  
1008 for antiepileptic activity. Lamotrigine also displayed inhibitory properties in the kindling model  
1009 in rats both during kindling development and in the fully kindled state. The relevance of these  
1010 models to human epilepsy, however, is not known.

1011 One proposed mechanism of action of lamotrigine, the relevance of which remains to be  
1012 established in humans, involves an effect on sodium channels. In vitro pharmacological studies  
1013 suggest that lamotrigine inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal  
1014 membranes and consequently modulating presynaptic transmitter release of excitatory amino  
1015 acids (e.g., glutamate and aspartate).

1016 Although the relevance for human use is unknown, the following data characterize the  
1017 performance of lamotrigine in receptor binding assays. Lamotrigine had a weak inhibitory effect  
1018 on the serotonin 5-HT<sub>3</sub> receptor (IC<sub>50</sub> = 18 μM). It does not exhibit high affinity binding  
1019 (IC<sub>50</sub>>100 μM) to the following neurotransmitter receptors: adenosine A<sub>1</sub> and A<sub>2</sub>; adrenergic α<sub>1</sub>,  
1020 α<sub>2</sub>, and β; dopamine D<sub>1</sub> and D<sub>2</sub>; γ-aminobutyric acid (GABA) A and B; histamine H<sub>1</sub>; kappa  
1021 opioid; muscarinic acetylcholine; and serotonin 5-HT<sub>2</sub>. Studies have failed to detect an effect of  
1022 lamotrigine on dihydropyridine-sensitive calcium channels. It had weak effects at sigma opioid  
1023 receptors (IC<sub>50</sub> = 145 μM). Lamotrigine did not inhibit the uptake of norepinephrine, dopamine,  
1024 or serotonin (IC<sub>50</sub>>200 μM) when tested in rat synaptosomes and/or human platelets in vitro.

1025 **Effect of Lamotrigine on N-Methyl d-Aspartate-Receptor Mediated Activity:**

1026 Lamotrigine did not inhibit N-methyl d-aspartate (NMDA)-induced depolarizations in rat cortical  
1027 slices or NMDA-induced cyclic GMP formation in immature rat cerebellum, nor did lamotrigine  
1028 displace compounds that are either competitive or noncompetitive ligands at this glutamate  
1029 receptor complex (CNQX, CGS, TCHP). The IC<sub>50</sub> for lamotrigine effects on NMDA-induced  
1030 currents (in the presence of 3 μM of glycine) in cultured hippocampal neurons exceeded 100  
1031 μM.

1032 The mechanisms by which lamotrigine exerts its therapeutic action in Bipolar Disorder  
1033 have not been established.

1034 **12.2 Pharmacodynamics**

1035 **Folate Metabolism:** In vitro, lamotrigine inhibited dihydrofolate reductase, the enzyme  
1036 that catalyzes the reduction of dihydrofolate to tetrahydrofolate. Inhibition of this enzyme may  
1037 interfere with the biosynthesis of nucleic acids and proteins. When oral daily doses of  
1038 lamotrigine were given to pregnant rats during organogenesis, fetal, placental, and maternal  
1039 folate concentrations were reduced. Significantly reduced concentrations of folate are associated  
1040 with teratogenesis [*see Use in Specific Populations (8.1)*]. Folate concentrations were also  
1041 reduced in male rats given repeated oral doses of lamotrigine. Reduced concentrations were  
1042 partially returned to normal when supplemented with folic acid.

1043 **Accumulation in Kidneys:** Lamotrigine accumulated in the kidney of the male rat,  
1044 causing chronic progressive nephrosis, necrosis, and mineralization. These findings are attributed  
1045 to α-2 microglobulin, a species- and sex-specific protein that has not been detected in humans or  
1046 other animal species.

1047 **Melanin Binding:** Lamotrigine binds to melanin-containing tissues, e.g., in the eye and  
1048 pigmented skin. It has been found in the uveal tract up to 52 weeks after a single dose in rodents.

1049 **Cardiovascular:** In dogs, lamotrigine is extensively metabolized to a 2-N-methyl  
1050 metabolite. This metabolite causes dose-dependent prolongations of the PR interval, widening of  
1051 the QRS complex, and, at higher doses, complete AV conduction block. Similar cardiovascular  
1052 effects are not anticipated in humans because only trace amounts of the 2-N-methyl metabolite  
1053 (<0.6% of lamotrigine dose) have been found in human urine [*see Clinical Pharmacology*  
1054 (12.3)]. However, it is conceivable that plasma concentrations of this metabolite could be

1055 increased in patients with a reduced capacity to glucuronidate lamotrigine (e.g., in patients with  
 1056 liver disease).

1057 **12.3 Pharmacokinetics**

1058 The pharmacokinetics of lamotrigine have been studied in patients with epilepsy, healthy  
 1059 young and elderly volunteers, and volunteers with chronic renal failure. Lamotrigine  
 1060 pharmacokinetic parameters for adult and pediatric patients and healthy normal volunteers are  
 1061 summarized in Tables 14 and 16.

1062

1063 **Table 14. Mean<sup>a</sup> Pharmacokinetic Parameters in Healthy Volunteers and Adult Patients**  
 1064 **With Epilepsy**

Adult Study Population	Number of Subjects	T <sub>max</sub> : Time of Maximum Plasma Concentration (hr)	t <sub>1/2</sub> : Elimination Half-life (hr)	Cl/F: Apparent Plasma Clearance (mL/min/kg)
<b>Healthy volunteers taking no other medications:</b>				
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)
<b>Healthy volunteers taking valproate:</b>				
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)
<b>Patients with epilepsy taking valproate only:</b>				
Single-dose LAMICTAL	4	4.8 (1.8-8.4)	58.8 (30.5-88.8)	0.28 (0.16-0.40)
<b>Patients with epilepsy taking carbamazepine, phenytoin, phenobarbital, or primidone<sup>b</sup> plus valproate:</b>				
Single-dose LAMICTAL	25	3.8 (1.0-10.0)	27.2 (11.2-51.6)	0.53 (0.27-1.04)

<b>Patients with epilepsy taking carbamazepine, phenytoin, phenobarbital, or primidone:<sup>b</sup></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)

1065 <sup>a</sup> The majority of parameter means determined in each study had coefficients of variation  
 1066 between 20% and 40% for half-life and CI/F and between 30% and 70% for T<sub>max</sub>. The overall  
 1067 mean values were calculated from individual study means that were weighted based on the  
 1068 number of volunteers/patients in each study. The numbers in parentheses below each  
 1069 parameter mean represent the range of individual volunteer/patient values across studies.

1070 <sup>b</sup> Carbamazepine, phenobarbital, phenytoin, and primidone have been shown to increase the  
 1071 apparent clearance of lamotrigine. Estrogen-containing oral contraceptives and other drugs  
 1072 such as rifampin that induce lamotrigine glucuronidation have also been shown to increase the  
 1073 apparent clearance of lamotrigine [*see Drug Interactions (7)*].  
 1074

1075 **Absorption:** Lamotrigine is rapidly and completely absorbed after oral administration  
 1076 with negligible first-pass metabolism (absolute bioavailability is 98%). The bioavailability is not  
 1077 affected by food. Peak plasma concentrations occur anywhere from 1.4 to 4.8 hours following  
 1078 drug administration. The lamotrigine chewable/dispersible tablets were found to be equivalent,  
 1079 whether they were administered as dispersed in water, chewed and swallowed, or swallowed as  
 1080 whole, to the lamotrigine compressed tablets in terms of rate and extent of absorption. In terms  
 1081 of rate and extent of absorption, lamotrigine orally disintegrating tablets whether disintegrated in  
 1082 the mouth or swallowed whole with water were equivalent to the lamotrigine compressed tablets  
 1083 swallowed with water.

1084 **Dose Proportionality:** In healthy volunteers not receiving any other medications and  
 1085 given single doses, the plasma concentrations of lamotrigine increased in direct proportion to the  
 1086 dose administered over the range of 50 to 400 mg. In 2 small studies (n = 7 and 8) of patients  
 1087 with epilepsy who were maintained on other AEDs, there also was a linear relationship between  
 1088 dose and lamotrigine plasma concentrations at steady state following doses of 50 to 350 mg  
 1089 twice daily.

1090 **Distribution:** Estimates of the mean apparent volume of distribution (Vd/F) of  
 1091 lamotrigine following oral administration ranged from 0.9 to 1.3 L/kg. Vd/F is independent of  
 1092 dose and is similar following single and multiple doses in both patients with epilepsy and in  
 1093 healthy volunteers.

1094 **Protein Binding:** Data from in vitro studies indicate that lamotrigine is approximately  
 1095 55% bound to human plasma proteins at plasma lamotrigine concentrations from 1 to 10 mcg/mL  
 1096 (10 mcg/mL is 4 to 6 times the trough plasma concentration observed in the controlled efficacy

1097 trials). Because lamotrigine is not highly bound to plasma proteins, clinically significant  
1098 interactions with other drugs through competition for protein binding sites are unlikely. The  
1099 binding of lamotrigine to plasma proteins did not change in the presence of therapeutic  
1100 concentrations of phenytoin, phenobarbital, or valproate. Lamotrigine did not displace other  
1101 AEDs (carbamazepine, phenytoin, phenobarbital) from protein-binding sites.

1102 **Metabolism:** Lamotrigine is metabolized predominantly by glucuronic acid conjugation;  
1103 the major metabolite is an inactive 2-N-glucuronide conjugate. After oral administration of 240  
1104 mg of <sup>14</sup>C-lamotrigine (15 μCi) to 6 healthy volunteers, 94% was recovered in the urine and 2%  
1105 was recovered in the feces. The radioactivity in the urine consisted of unchanged lamotrigine  
1106 (10%), the 2-N-glucuronide (76%), a 5-N-glucuronide (10%), a 2-N-methyl metabolite (0.14%),  
1107 and other unidentified minor metabolites (4%).

1108 **Enzyme Induction:** The effects of lamotrigine on the induction of specific families of  
1109 mixed-function oxidase isozymes have not been systematically evaluated.

1110 Following multiple administrations (150 mg twice daily) to normal volunteers taking no  
1111 other medications, lamotrigine induced its own metabolism, resulting in a 25% decrease in t<sub>1/2</sub> and  
1112 a 37% increase in Cl/F at steady state compared with values obtained in the same volunteers  
1113 following a single dose. Evidence gathered from other sources suggests that self-induction by  
1114 lamotrigine may not occur when lamotrigine is given as adjunctive therapy in patients receiving  
1115 enzyme-inducing drugs such as carbamazepine, phenytoin, phenobarbital, primidone, or drugs  
1116 such as rifampin that induce lamotrigine glucuronidation [*see Drug Interactions (7)*].

1117 **Elimination:** The elimination half-life and apparent clearance of lamotrigine following  
1118 administration of LAMICTAL to adult patients with epilepsy and healthy volunteers is  
1119 summarized in Table 14. Half-life and apparent oral clearance vary depending on concomitant  
1120 AEDs.

1121 **Drug Interactions:** The apparent clearance of lamotrigine is affected by the  
1122 coadministration of certain medications [*see Warnings and Precautions (5.8, 5.12), Drug*  
1123 *Interactions (7)*].

1124 The net effects of drug interactions with LAMICTAL are summarized in Tables 13 and  
1125 15, followed by details of the drug interaction studies below.  
1126

1127 **Table 15. Summary of Drug Interactions With LAMICTAL**

Drug	Drug Plasma Concentration With Adjunctive LAMICTAL <sup>a</sup>	Lamotrigine Plasma Concentration With Adjunctive Drugs <sup>b</sup>
Oral contraceptives (e.g., ethinylestradiol/levonorgestrel) <sup>c</sup>	↔ <sup>d</sup>	↓
Bupropion	Not assessed	↔
Carbamazepine (CBZ)	↔	↓
CBZ epoxide <sup>e</sup>	?	
Felbamate	Not assessed	↔
Gabapentin	Not assessed	↔
Levetiracetam	↔	↔
Lithium	↔	Not assessed
Olanzapine	↔	↔ <sup>f</sup>
Oxcarbazepine	↔	↔
10-monohydroxy oxcarbazepine metabolite <sup>g</sup>	↔	
Phenobarbital/primidone	↔	↓
Phenytoin (PHT)	↔	↓
Pregabalin	↔	↔
Rifampin	Not assessed	↓
Topiramate	↔ <sup>h</sup>	↔
Valproate	↓	↑
Valproate + PHT and/or CBZ	Not assessed	↔
Zonisamide	Not assessed	↔

1128 <sup>a</sup> From adjunctive clinical trials and volunteer studies.

1129 <sup>b</sup> Net effects were estimated by comparing the mean clearance values obtained in adjunctive  
 1130 clinical trials and volunteer studies.

1131 <sup>c</sup> The effect of other hormonal contraceptive preparations or hormone replacement therapy on  
 1132 the pharmacokinetics of lamotrigine has not been systematically evaluated in clinical trials,  
 1133 although the effect may be similar to that seen with the ethinylestradiol/levonorgestrel  
 1134 combinations.

1135 <sup>d</sup> Modest decrease in levonorgestrel.

1136 <sup>e</sup> Not administered, but an active metabolite of carbamazepine.

1137 <sup>f</sup> Slight decrease, not expected to be clinically relevant.

1138 <sup>g</sup> Not administered, but an active metabolite of oxcarbazepine.

1139 <sup>h</sup> Slight increase, not expected to be clinically relevant.

1140 ↔ = No significant effect.

1141 ? = Conflicting data.

1142

1143 **Estrogen-Containing Oral Contraceptives:** In 16 female volunteers, an oral  
1144 contraceptive preparation containing 30 mcg ethinylestradiol and 150 mcg levonorgestrel  
1145 increased the apparent clearance of lamotrigine (300 mg/day) by approximately 2-fold with mean  
1146 decreases in AUC of 52% and in  $C_{max}$  of 39%. In this study, trough serum lamotrigine  
1147 concentrations gradually increased and were approximately 2-fold higher on average at the end  
1148 of the week of the inactive hormone preparation compared with trough lamotrigine  
1149 concentrations at the end of the active hormone cycle.

1150 Gradual transient increases in lamotrigine plasma levels (approximate 2-fold increase)  
1151 occurred during the week of inactive hormone preparation (“pill-free” week) for women not also  
1152 taking a drug that increased the clearance of lamotrigine (carbamazepine, phenytoin,  
1153 phenobarbital, primidone, or other drugs such as rifampin that induce lamotrigine  
1154 glucuronidation [*see Drug Interactions (7)*]). The increase in lamotrigine plasma levels will be  
1155 greater if the dose of LAMICTAL is increased in the few days before or during the “pill-free”  
1156 week. Increases in lamotrigine plasma levels could result in dose-dependent adverse reactions.

1157 In the same study, coadministration of LAMICTAL (300 mg/day) in 16 female  
1158 volunteers did not affect the pharmacokinetics of the ethinylestradiol component of the oral  
1159 contraceptive preparation. There were mean decreases in the AUC and  $C_{max}$  of the levonorgestrel  
1160 component of 19% and 12%, respectively. Measurement of serum progesterone indicated that  
1161 there was no hormonal evidence of ovulation in any of the 16 volunteers, although measurement  
1162 of serum FSH, LH, and estradiol indicated that there was some loss of suppression of the  
1163 hypothalamic-pituitary-ovarian axis.

1164 The effects of doses of LAMICTAL other than 300 mg/day have not been systematically  
1165 evaluated in controlled clinical trials.

1166 The clinical significance of the observed hormonal changes on ovulatory activity is  
1167 unknown. However, the possibility of decreased contraceptive efficacy in some patients cannot  
1168 be excluded. Therefore, patients should be instructed to promptly report changes in their  
1169 menstrual pattern (e.g., break-through bleeding).

1170 Dosage adjustments may be necessary for women receiving estrogen-containing oral  
1171 contraceptive preparations [*see Dosage and Administration (2.1)*].

1172 **Other Hormonal Contraceptives or Hormone Replacement Therapy:** The effect of  
1173 other hormonal contraceptive preparations or hormone replacement therapy on the  
1174 pharmacokinetics of lamotrigine has not been systematically evaluated. It has been reported that  
1175 ethinylestradiol, not progestogens, increased the clearance of lamotrigine up to 2-fold, and the  
1176 progestin-only pills had no effect on lamotrigine plasma levels. Therefore, adjustments to the  
1177 dosage of LAMICTAL in the presence of progestogens alone will likely not be needed.

1178 **Bupropion:** The pharmacokinetics of a 100-mg single dose of LAMICTAL in healthy  
1179 volunteers (n = 12) were not changed by coadministration of bupropion sustained-release  
1180 formulation (150 mg twice daily) starting 11 days before LAMICTAL.

1181            **Carbamazepine:** LAMICTAL has no appreciable effect on steady-state carbamazepine  
1182 plasma concentration. Limited clinical data suggest there is a higher incidence of dizziness,  
1183 diplopia, ataxia, and blurred vision in patients receiving carbamazepine with lamotrigine than in  
1184 patients receiving other AEDs with lamotrigine [*see Adverse Reactions (6.1)*]. The mechanism  
1185 of this interaction is unclear. The effect of lamotrigine on plasma concentrations of  
1186 carbamazepine-epoxide is unclear. In a small subset of patients (n = 7) studied in a placebo-  
1187 controlled trial, lamotrigine had no effect on carbamazepine-epoxide plasma concentrations, but  
1188 in a small, uncontrolled study (n = 9), carbamazepine-epoxide levels increased.

1189            The addition of carbamazepine decreases lamotrigine steady-state concentrations by  
1190 approximately 40%.

1191            **Felbamate:** In a study of 21 healthy volunteers, coadministration of felbamate (1,200 mg  
1192 twice daily) with lamotrigine (100 mg twice daily for 10 days) appeared to have no clinically  
1193 relevant effects on the pharmacokinetics of lamotrigine.

1194            **Folate Inhibitors:** Lamotrigine is a weak inhibitor of dihydrofolate reductase. Prescribers  
1195 should be aware of this action when prescribing other medications that inhibit folate metabolism.

1196            **Gabapentin:** Based on a retrospective analysis of plasma levels in 34 patients who  
1197 received lamotrigine both with and without gabapentin, gabapentin does not appear to change the  
1198 apparent clearance of lamotrigine.

1199            **Levetiracetam:** Potential drug interactions between levetiracetam and lamotrigine were  
1200 assessed by evaluating serum concentrations of both agents during placebo-controlled clinical  
1201 trials. These data indicate that lamotrigine does not influence the pharmacokinetics of  
1202 levetiracetam and that levetiracetam does not influence the pharmacokinetics of lamotrigine.

1203            **Lithium:** The pharmacokinetics of lithium were not altered in healthy subjects (n = 20) by  
1204 coadministration of lamotrigine (100 mg/day) for 6 days.

1205            **Olanzapine:** The AUC and C<sub>max</sub> of olanzapine were similar following the addition of  
1206 olanzapine (15 mg once daily) to lamotrigine (200 mg once daily) in healthy male volunteers (n  
1207 = 16) compared with the AUC and C<sub>max</sub> in healthy male volunteers receiving olanzapine alone (n  
1208 = 16).

1209            In the same study, the AUC and C<sub>max</sub> of lamotrigine were reduced on average by 24%  
1210 and 20%, respectively, following the addition of olanzapine to lamotrigine in healthy male  
1211 volunteers compared with those receiving lamotrigine alone. This reduction in lamotrigine  
1212 plasma concentrations is not expected to be clinically relevant.

1213            **Oxcarbazepine:** The AUC and C<sub>max</sub> of oxcarbazepine and its active 10-monohydroxy  
1214 oxcarbazepine metabolite were not significantly different following the addition of  
1215 oxcarbazepine (600 mg twice daily) to lamotrigine (200 mg once daily) in healthy male  
1216 volunteers (n = 13) compared with healthy male volunteers receiving oxcarbazepine alone (n =  
1217 13).

1218            In the same study, the AUC and C<sub>max</sub> of lamotrigine were similar following the addition  
1219 of oxcarbazepine (600 mg twice daily) to LAMICTAL in healthy male volunteers compared with

1220 those receiving LAMICTAL alone. Limited clinical data suggest a higher incidence of headache,  
1221 dizziness, nausea, and somnolence with coadministration of lamotrigine and oxcarbazepine  
1222 compared with lamotrigine alone or oxcarbazepine alone.

1223 Phenobarbital, Primidone: The addition of phenobarbital or primidone decreases  
1224 lamotrigine steady-state concentrations by approximately 40%.

1225 Phenytoin: Lamotrigine has no appreciable effect on steady-state phenytoin plasma  
1226 concentrations in patients with epilepsy. The addition of phenytoin decreases lamotrigine steady-  
1227 state concentrations by approximately 40%.

1228 Pregabalin: Steady-state trough plasma concentrations of lamotrigine were not affected  
1229 by concomitant pregabalin (200 mg 3 times daily) administration. There are no pharmacokinetic  
1230 interactions between lamotrigine and pregabalin.

1231 Rifampin: In 10 male volunteers, rifampin (600 mg/day for 5 days) significantly  
1232 increased the apparent clearance of a single 25-mg dose of lamotrigine by approximately 2-fold  
1233 (AUC decreased by approximately 40%).

1234 Topiramate: Topiramate resulted in no change in plasma concentrations of lamotrigine.  
1235 Administration of lamotrigine resulted in a 15% increase in topiramate concentrations.

1236 Valproate: When lamotrigine was administered to healthy volunteers (n = 18) receiving  
1237 valproate, the trough steady-state valproate plasma concentrations decreased by an average of  
1238 25% over a 3-week period, and then stabilized. However, adding lamotrigine to the existing  
1239 therapy did not cause a change in valproate plasma concentrations in either adult or pediatric  
1240 patients in controlled clinical trials.

1241 The addition of valproate increased lamotrigine steady-state concentrations in normal  
1242 volunteers by slightly more than 2-fold. In one study, maximal inhibition of lamotrigine  
1243 clearance was reached at valproate doses between 250 and 500 mg/day and did not increase as  
1244 the valproate dose was further increased.

1245 Zonisamide: In a study of 18 patients with epilepsy, coadministration of zonisamide  
1246 (200 to 400 mg/day) with lamotrigine (150 to 500 mg/day for 35 days) had no significant effect  
1247 on the pharmacokinetics of lamotrigine.

1248 Known Inducers or Inhibitors of Glucuronidation: Drugs other than those listed above  
1249 have not been systematically evaluated in combination with lamotrigine. Since lamotrigine is  
1250 metabolized predominately by glucuronic acid conjugation, drugs that are known to induce or  
1251 inhibit glucuronidation may affect the apparent clearance of lamotrigine and doses of lamotrigine  
1252 may require adjustment based on clinical response.

1253 Other: Results of in vitro experiments suggest that clearance of lamotrigine is unlikely to  
1254 be reduced by concomitant administration of amitriptyline, clonazepam, clozapine, fluoxetine,  
1255 haloperidol, lorazepam, phenelzine, risperidone, sertraline, or trazodone.

1256 Results of in vitro experiments suggest that lamotrigine does not reduce the clearance of  
1257 drugs eliminated predominantly by CYP2D6.

1258            **Special Populations: *Patients With Renal Impairment:*** Twelve volunteers with  
1259 chronic renal failure (mean creatinine clearance: 13 mL/min, range: 6 to 23) and another 6  
1260 individuals undergoing hemodialysis were each given a single 100-mg dose of lamotrigine. The  
1261 mean plasma half-lives determined in the study were 42.9 hours (chronic renal failure), 13.0  
1262 hours (during hemodialysis), and 57.4 hours (between hemodialysis) compared with 26.2 hours  
1263 in healthy volunteers. On average, approximately 20% (range: 5.6 to 35.1) of the amount of  
1264 lamotrigine present in the body was eliminated by hemodialysis during a 4-hour session [*see*  
1265 *Dosage and Administration (2.1)*].

1266            **Hepatic Disease:** The pharmacokinetics of lamotrigine following a single 100-mg  
1267 dose of lamotrigine were evaluated in 24 subjects with mild, moderate, and severe hepatic  
1268 impairment (Child-Pugh Classification system) and compared with 12 subjects without hepatic  
1269 impairment. The patients with severe hepatic impairment were without ascites (n = 2) or with  
1270 ascites (n = 5). The mean apparent clearances of lamotrigine in patients with mild (n = 12),  
1271 moderate (n = 5), severe without ascites (n = 2), and severe with ascites (n = 5) liver impairment  
1272 were  $0.30 \pm 0.09$ ,  $0.24 \pm 0.1$ ,  $0.21 \pm 0.04$ , and  $0.15 \pm 0.09$  mL/min/kg, respectively, as compared  
1273 with  $0.37 \pm 0.1$  mL/min/kg in the healthy controls. Mean half-lives of lamotrigine in patients  
1274 with mild, moderate, severe without ascites, and severe with ascites hepatic impairment were  $46$   
1275  $\pm 20$ ,  $72 \pm 44$ ,  $67 \pm 11$ , and  $100 \pm 48$  hours, respectively, as compared with  $33 \pm 7$  hours in  
1276 healthy controls [*see Dosage and Administration (2.1)*].

1277            **Age: *Pediatric Patients:*** The pharmacokinetics of lamotrigine following a single 2-  
1278 mg/kg dose were evaluated in 2 studies of pediatric patients (n = 29 for patients 10 months to 5.9  
1279 years of age and n = 26 for patients 5 to 11 years of age). Forty-three patients received  
1280 concomitant therapy with other AEDs and 12 patients received lamotrigine as monotherapy.  
1281 Lamotrigine pharmacokinetic parameters for pediatric patients are summarized in Table 16.

1282            Population pharmacokinetic analyses involving patients 2 to 18 years of age  
1283 demonstrated that lamotrigine clearance was influenced predominantly by total body weight and  
1284 concurrent AED therapy. The oral clearance of lamotrigine was higher, on a body weight basis,  
1285 in pediatric patients than in adults. Weight-normalized lamotrigine clearance was higher in those  
1286 subjects weighing less than 30 kg, compared with those weighing greater than 30 kg.  
1287 Accordingly, patients weighing less than 30 kg may need an increase of as much as 50% in  
1288 maintenance doses, based on clinical response, as compared with subjects weighing more than  
1289 30 kg being administered the same AEDs [*see Dosage and Administration (2.2)*]. These analyses  
1290 also revealed that, after accounting for body weight, lamotrigine clearance was not significantly  
1291 influenced by age. Thus, the same weight-adjusted doses should be administered to children  
1292 irrespective of differences in age. Concomitant AEDs which influence lamotrigine clearance in  
1293 adults were found to have similar effects in children.

1294

1295

**Table 16. Mean Pharmacokinetic Parameters in Pediatric Patients With Epilepsy**

Pediatric Study Population	Number of Subjects	T <sub>max</sub> (hr)	t <sub>1/2</sub> (hr)	Cl/F (mL/min/kg)
<b>Ages 10 months-5.3 years</b>				
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone <sup>a</sup>	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)
<b>Ages 5-11 years</b>				
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone <sup>a</sup>	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 <sup>a</sup> 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 <sup>b</sup>	3	4.5 (3.0-6.0)	65.8 (50.7-73.7)	0.24 (0.21-0.26)
<b>Ages 13-18 years</b>				
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone <sup>a</sup>	11	c	c	1.3
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone <sup>a</sup> plus valproate	8	c	c	0.5
Patients taking valproate only	4	c	c	0.3

1296 <sup>a</sup> Carbamazepine, phenobarbital, phenytoin, and primidone have been shown to increase the  
 1297 apparent clearance of lamotrigine. Estrogen-containing oral contraceptives and rifampin have  
 1298 also been shown to increase the apparent clearance of lamotrigine [see Drug Interactions (7)].

1299 <sup>b</sup> Two subjects were included in the calculation for mean T<sub>max</sub>.

1300 <sup>c</sup> Parameter not estimated.

1301  
 1302 *Elderly:* The pharmacokinetics of lamotrigine following a single 150-mg dose of  
 1303 LAMICTAL were evaluated in 12 elderly volunteers between the ages of 65 and 76 years (mean  
 1304 creatinine clearance = 61 mL/min, range: 33 to 108 mL/min). The mean half-life of lamotrigine

1305 in these subjects was 31.2 hours (range: 24.5 to 43.4 hours), and the mean clearance was 0.40  
1306 mL/min/kg (range: 0.26 to 0.48 mL/min/kg).

1307 *Gender:* The clearance of lamotrigine is not affected by gender. However, during  
1308 dose escalation of LAMICTAL in one clinical trial in patients with epilepsy on a stable dose of  
1309 valproate (n = 77), mean trough lamotrigine concentrations, unadjusted for weight, were 24% to  
1310 45% higher (0.3 to 1.7 mcg/mL) in females than in males.

1311 *Race:* The apparent oral clearance of lamotrigine was 25% lower in non-Caucasians  
1312 than Caucasians.

### 1313 **13 NONCLINICAL TOXICOLOGY**

#### 1314 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

1315 No evidence of carcinogenicity was seen in 1 mouse study or 2 rat studies following oral  
1316 administration of lamotrigine for up to 2 years at maximum tolerated doses (30 mg/kg/day for  
1317 mice and 10 to 15 mg/kg/day for rats, doses that are equivalent to 90 mg/m<sup>2</sup> and 60 to 90 mg/m<sup>2</sup>,  
1318 respectively). Steady-state plasma concentrations ranged from 1 to 4 mcg/mL in the mouse study  
1319 and 1 to 10 mcg/mL in the rat study. Plasma concentrations associated with the recommended  
1320 human doses of 300 to 500 mg/day are generally in the range of 2 to 5 mcg/mL, but  
1321 concentrations as high as 19 mcg/mL have been recorded.

1322 Lamotrigine was not mutagenic in the presence or absence of metabolic activation when  
1323 tested in 2 gene mutation assays (the Ames test and the in vitro mammalian mouse lymphoma  
1324 assay). In 2 cytogenetic assays (the in vitro human lymphocyte assay and the in vivo rat bone  
1325 marrow assay), lamotrigine did not increase the incidence of structural or numerical  
1326 chromosomal abnormalities.

1327 No evidence of impairment of fertility was detected in rats given oral doses of  
1328 lamotrigine up to 2.4 times the highest usual human maintenance dose of 8.33 mg/kg/day or 0.4  
1329 times the human dose on a mg/m<sup>2</sup> basis. The effect of lamotrigine on human fertility is unknown.

### 1330 **14 CLINICAL STUDIES**

#### 1331 **14.1 Epilepsy**

1332 Monotherapy With LAMICTAL in Adults With Partial Seizures Already Receiving  
1333 Treatment With Carbamazepine, Phenytoin, Phenobarbital, or Primidone as the Single  
1334 Antiepileptic Drug: The effectiveness of monotherapy with LAMICTAL was established in a  
1335 multicenter, double-blind clinical trial enrolling 156 adult outpatients with partial seizures. The  
1336 patients experienced at least 4 simple partial, complex partial, and/or secondarily generalized  
1337 seizures during each of 2 consecutive 4-week periods while receiving carbamazepine or  
1338 phenytoin monotherapy during baseline. LAMICTAL (target dose of 500 mg/day) or valproate  
1339 (1,000 mg/day) was added to either carbamazepine or phenytoin monotherapy over a 4-week  
1340 period. Patients were then converted to monotherapy with LAMICTAL or valproate during the  
1341 next 4 weeks, then continued on monotherapy for an additional 12-week period.

1342 Study endpoints were completion of all weeks of study treatment or meeting an escape  
1343 criterion. Criteria for escape relative to baseline were: (1) doubling of average monthly seizure  
1344 count, (2) doubling of highest consecutive 2-day seizure frequency, (3) emergence of a new  
1345 seizure type (defined as a seizure that did not occur during the 8-week baseline) that is more  
1346 severe than seizure types that occur during study treatment, or (4) clinically significant  
1347 prolongation of generalized tonic-clonic seizures. The primary efficacy variable was the  
1348 proportion of patients in each treatment group who met escape criteria.

1349 The percentages of patients who met escape criteria were 42% (32/76) in the group  
1350 receiving LAMICTAL and 69% (55/80) in the valproate group. The difference in the percentage  
1351 of patients meeting escape criteria was statistically significant ( $P = 0.0012$ ) in favor of  
1352 LAMICTAL. No differences in efficacy based on age, sex, or race were detected.

1353 Patients in the control group were intentionally treated with a relatively low dose of  
1354 valproate; as such, the sole objective of this study was to demonstrate the effectiveness and  
1355 safety of monotherapy with LAMICTAL, and cannot be interpreted to imply the superiority of  
1356 LAMICTAL to an adequate dose of valproate.

1357 Adjunctive Therapy With LAMICTAL in Adults With Partial Seizures: The  
1358 effectiveness of LAMICTAL as adjunctive therapy (added to other AEDs) was established in 3  
1359 multicenter, placebo-controlled, double-blind clinical trials in 355 adults with refractory partial  
1360 seizures. The patients had a history of at least 4 partial seizures per month in spite of receiving  
1361 one or more AEDs at therapeutic concentrations and, in 2 of the studies, were observed on their  
1362 established AED regimen during baselines that varied between 8 to 12 weeks. In the third,  
1363 patients were not observed in a prospective baseline. In patients continuing to have at least 4  
1364 seizures per month during the baseline, LAMICTAL or placebo was then added to the existing  
1365 therapy. In all 3 studies, change from baseline in seizure frequency was the primary measure of  
1366 effectiveness. The results given below are for all partial seizures in the intent-to-treat population  
1367 (all patients who received at least one dose of treatment) in each study, unless otherwise  
1368 indicated. The median seizure frequency at baseline was 3 per week while the mean at baseline  
1369 was 6.6 per week for all patients enrolled in efficacy studies.

1370 One study ( $n = 216$ ) was a double-blind, placebo-controlled, parallel trial consisting of a  
1371 24-week treatment period. Patients could not be on more than 2 other anticonvulsants and  
1372 valproate was not allowed. Patients were randomized to receive placebo, a target dose of 300  
1373 mg/day of LAMICTAL, or a target dose of 500 mg/day of LAMICTAL. The median reductions  
1374 in the frequency of all partial seizures relative to baseline were 8% in patients receiving placebo,  
1375 20% in patients receiving 300 mg/day of LAMICTAL, and 36% in patients receiving 500  
1376 mg/day of LAMICTAL. The seizure frequency reduction was statistically significant in the 500-  
1377 mg/day group compared with the placebo group, but not in the 300-mg/day group.

1378 A second study ( $n = 98$ ) was a double-blind, placebo-controlled, randomized, crossover  
1379 trial consisting of two 14-week treatment periods (the last 2 weeks of which consisted of dose  
1380 tapering) separated by a 4-week washout period. Patients could not be on more than 2 other

1381 anticonvulsants and valproate was not allowed. The target dose of LAMICTAL was 400 mg/day.  
1382 When the first 12 weeks of the treatment periods were analyzed, the median change in seizure  
1383 frequency was a 25% reduction on LAMICTAL compared with placebo ( $P<0.001$ ).

1384 The third study ( $n = 41$ ) was a double-blind, placebo-controlled, crossover trial consisting  
1385 of two 12-week treatment periods separated by a 4-week washout period. Patients could not be  
1386 on more than 2 other anticonvulsants. Thirteen patients were on concomitant valproate; these  
1387 patients received 150 mg/day of LAMICTAL. The 28 other patients had a target dose of 300  
1388 mg/day of LAMICTAL. The median change in seizure frequency was a 26% reduction on  
1389 LAMICTAL compared with placebo ( $P<0.01$ ).

1390 No differences in efficacy based on age, sex, or race, as measured by change in seizure  
1391 frequency, were detected.

1392 Adjunctive Therapy With LAMICTAL in Pediatric Patients With Partial Seizures:

1393 The effectiveness of LAMICTAL as adjunctive therapy in pediatric patients with partial seizures  
1394 was established in a multicenter, double-blind, placebo-controlled trial in 199 patients 2 to 16  
1395 years of age ( $n = 98$  on LAMICTAL,  $n = 101$  on placebo). Following an 8-week baseline phase,  
1396 patients were randomized to 18 weeks of treatment with LAMICTAL or placebo added to their  
1397 current AED regimen of up to 2 drugs. Patients were dosed based on body weight and valproate  
1398 use. Target doses were designed to approximate 5 mg/kg/day for patients taking valproate  
1399 (maximum dose: 250 mg/day) and 15 mg/kg/day for the patients not taking valproate (maximum  
1400 dose: 750 mg/day). The primary efficacy endpoint was percentage change from baseline in all  
1401 partial seizures. For the intent-to-treat population, the median reduction of all partial seizures  
1402 was 36% in patients treated with LAMICTAL and 7% on placebo, a difference that was  
1403 statistically significant ( $P<0.01$ ).

1404 Adjunctive Therapy With LAMICTAL in Pediatric and Adult Patients With Lennox-

1405 Gastaut Syndrome: The effectiveness of LAMICTAL as adjunctive therapy in patients with  
1406 Lennox-Gastaut syndrome was established in a multicenter, double-blind, placebo-controlled  
1407 trial in 169 patients 3 to 25 years of age ( $n = 79$  on LAMICTAL,  $n = 90$  on placebo). Following a  
1408 4-week single-blind, placebo phase, patients were randomized to 16 weeks of treatment with  
1409 LAMICTAL or placebo added to their current AED regimen of up to 3 drugs. Patients were  
1410 dosed on a fixed-dose regimen based on body weight and valproate use. Target doses were  
1411 designed to approximate 5 mg/kg/day for patients taking valproate (maximum dose: 200 mg/day)  
1412 and 15 mg/kg/day for patients not taking valproate (maximum dose: 400 mg/day). The primary  
1413 efficacy endpoint was percentage change from baseline in major motor seizures (atonic, tonic,  
1414 major myoclonic, and tonic-clonic seizures). For the intent-to-treat population, the median  
1415 reduction of major motor seizures was 32% in patients treated with LAMICTAL and 9% on  
1416 placebo, a difference that was statistically significant ( $P<0.05$ ). Drop attacks were significantly  
1417 reduced by LAMICTAL (34%) compared with placebo (9%), as were tonic-clonic seizures (36%  
1418 reduction versus 10% increase for LAMICTAL and placebo, respectively).

1419 Adjunctive Therapy With LAMICTAL in Pediatric and Adult Patients With Primary  
1420 Generalized Tonic-Clonic Seizures: The effectiveness of LAMICTAL as adjunctive therapy  
1421 in patients with primary generalized tonic-clonic seizures was established in a multicenter,  
1422 double-blind, placebo-controlled trial in 117 pediatric and adult patients  $\geq 2$  years ( $n = 58$  on  
1423 LAMICTAL,  $n = 59$  on placebo). Patients with at least 3 primary generalized tonic-clonic  
1424 seizures during an 8-week baseline phase were randomized to 19 to 24 weeks of treatment with  
1425 LAMICTAL or placebo added to their current AED regimen of up to 2 drugs. Patients were  
1426 dosed on a fixed-dose regimen, with target doses ranging from 3 mg/kg/day to 12 mg/kg/day for  
1427 pediatric patients and from 200 mg/day to 400 mg/day for adult patients based on concomitant  
1428 AED.

1429 The primary efficacy endpoint was percentage change from baseline in primary  
1430 generalized tonic-clonic seizures. For the intent-to-treat population, the median percent reduction  
1431 of primary generalized tonic-clonic seizures was 66% in patients treated with LAMICTAL and  
1432 34% on placebo, a difference that was statistically significant ( $P = 0.006$ ).

#### 1433 **14.2 Bipolar Disorder**

1434 The effectiveness of LAMICTAL in the maintenance treatment of Bipolar I Disorder was  
1435 established in 2 multicenter, double-blind, placebo-controlled studies in adult patients who met  
1436 DSM-IV criteria for Bipolar I Disorder. Study 1 enrolled patients with a current or recent (within  
1437 60 days) depressive episode as defined by DSM-IV and Study 2 included patients with a current  
1438 or recent (within 60 days) episode of mania or hypomania as defined by DSM-IV. Both studies  
1439 included a cohort of patients (30% of 404 patients in Study 1 and 28% of 171 patients in Study  
1440 2) with rapid cycling Bipolar Disorder (4 to 6 episodes per year).

1441 In both studies, patients were titrated to a target dose of 200 mg of LAMICTAL, as add-  
1442 on therapy or as monotherapy, with gradual withdrawal of any psychotropic medications during  
1443 an 8- to 16-week open-label period. Overall 81% of 1,305 patients participating in the open-label  
1444 period were receiving 1 or more other psychotropic medications, including benzodiazepines,  
1445 selective serotonin reuptake inhibitors (SSRIs), atypical antipsychotics (including olanzapine),  
1446 valproate, or lithium, during titration of LAMICTAL. Patients with a CGI-severity score of 3 or  
1447 less maintained for at least 4 continuous weeks, including at least the final week on monotherapy  
1448 with LAMICTAL, were randomized to a placebo-controlled, double-blind treatment period for  
1449 up to 18 months. The primary endpoint was TIME (time to intervention for a mood episode or  
1450 one that was emerging, time to discontinuation for either an adverse event that was judged to be  
1451 related to Bipolar Disorder, or for lack of efficacy). The mood episode could be depression,  
1452 mania, hypomania, or a mixed episode.

1453 In Study 1, patients received double-blind monotherapy with LAMICTAL 50 mg/day ( $n$   
1454 = 50), LAMICTAL 200 mg/day ( $n = 124$ ), LAMICTAL 400 mg/day ( $n = 47$ ), or placebo ( $n =$   
1455 121). LAMICTAL (200- and 400-mg/day treatment groups combined) was superior to placebo in  
1456 delaying the time to occurrence of a mood episode. Separate analyses of the 200- and 400-  
1457 mg/day dose groups revealed no added benefit from the higher dose.

1458 In Study 2, patients received double-blind monotherapy with LAMICTAL (100 to 400  
1459 mg/day, n = 59), or placebo (n = 70). LAMICTAL was superior to placebo in delaying time to  
1460 occurrence of a mood episode. The mean dose of LAMICTAL was about 211 mg/day.

1461 Although these studies were not designed to separately evaluate time to the occurrence of  
1462 depression or mania, a combined analysis for the 2 studies revealed a statistically significant  
1463 benefit for LAMICTAL over placebo in delaying the time to occurrence of both depression and  
1464 mania, although the finding was more robust for depression.

## 1465 **16 HOW SUPPLIED/STORAGE AND HANDLING**

### 1466 **LAMICTAL (lamotrigine) Tablets**

1467 25 mg, white, scored, shield-shaped tablets debossed with “LAMICTAL” and “25”,  
1468 bottles of 100 (NDC 0173-0633-02).

1469 Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled  
1470 Room Temperature] in a dry place.

1471 100 mg, peach, scored, shield-shaped tablets debossed with “LAMICTAL” and “100”,  
1472 bottles of 100 (NDC 0173-0642-55).

1473 150 mg, cream, scored, shield-shaped tablets debossed with “LAMICTAL” and “150”,  
1474 bottles of 60 (NDC 0173-0643-60).

1475 200 mg, blue, scored, shield-shaped tablets debossed with “LAMICTAL” and “200”,  
1476 bottles of 60 (NDC 0173-0644-60).

1477 Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled  
1478 Room Temperature] in a dry place and protect from light.

1479

### 1480 **LAMICTAL (lamotrigine) Starter Kit for Patients Taking Valproate (Blue Kit)**

1481 25 mg, white, scored, shield-shaped tablets debossed with “LAMICTAL” and “25”,  
1482 blisterpack of 35 tablets (NDC 0173-0633-10).

1483 Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled  
1484 Room Temperature] in a dry place.

### 1485 **LAMICTAL (lamotrigine) Starter Kit for Patients Taking Carbamazepine, 1486 Phenytoin, Phenobarbital, or Primidone and Not Taking Valproate (Green Kit)**

1487 25 mg, white, scored, shield-shaped tablets debossed with “LAMICTAL” and “25” and  
1488 100 mg, peach, scored, shield-shaped tablets debossed with “LAMICTAL” and “100”,  
1489 blisterpack of 98 tablets (84/25-mg tablets and 14/100-mg tablets) (NDC 0173-0817-28).

1490 Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled  
1491 Room Temperature] in a dry place and protect from light.

### 1492 **LAMICTAL (lamotrigine) Starter Kit for Patients Not Taking Carbamazepine, 1493 Phenytoin, Phenobarbital, Primidone, or Valproate (Orange Kit)**

1494 25 mg, white, scored, shield-shaped tablets debossed with “LAMICTAL” and “25” and  
1495 100 mg, peach, scored, shield-shaped tablets debossed with “LAMICTAL” and “100”,  
1496 blisterpack of 49 tablets (42/25-mg tablets and 7/100-mg tablets) (NDC 0173-0594-02).

1497 Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled  
1498 Room Temperature] in a dry place and protect from light.

1499

1500 **LAMICTAL (lamotrigine) Chewable Dispersible Tablets**

1501 2 mg, white to off-white, round tablets debossed with “LTG” over “2”, bottles of 30  
1502 (NDC 0173-0699-00). ORDER DIRECTLY FROM GlaxoSmithKline 1-800-334-4153.

1503 5 mg, white to off-white, caplet-shaped tablets debossed with “GX CL2”, bottles of 100  
1504 (NDC 0173-0526-00).

1505 25 mg, white, super elliptical-shaped tablets debossed with “GX CL5”, bottles of 100  
1506 (NDC 0173-0527-00).

1507 Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled  
1508 Room Temperature] in a dry place.

1509

1510 **LAMICTAL ODT (lamotrigine) Orally Disintegrating Tablets**

1511 25 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with “LMT”  
1512 on one side and “25” on the other, Maintenance Packs of 30 (NDC 0173-0772-02).

1513 50 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with “LMT”  
1514 on one side and “50” on the other, Maintenance Packs of 30 (NDC 0173-0774-02).

1515 100 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with  
1516 “LAMICTAL” on one side and “100” on the other, Maintenance Packs of 30 (NDC 0173-0776-  
1517 02).

1518 200 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with  
1519 “LAMICTAL” on one side and “200” on the other, Maintenance Packs of 30 (NDC 0173-0777-  
1520 02).

1521 Store between 20°C to 25°C (68°F to 77°F); with excursions permitted between 15°C and  
1522 30°C (59°F and 86°F).

1523 **LAMICTAL ODT (lamotrigine) Patient Titration Kit for Patients Taking Valproate**  
1524 **(Blue ODT Kit)**

1525 25 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with “LMT”  
1526 on one side and “25” on the other, and 50 mg, white to off-white, round, flat-faced, radius edge,  
1527 tablets debossed with “LMT” on one side and “50” on the other, blisterpack of 28 tablets  
1528 (21/25-mg tablets and 7/50-mg tablets) (NDC 0173-0779-00).

1529 **LAMICTAL ODT (lamotrigine) Patient Titration Kit for Patients Taking**  
1530 **Carbamazepine, Phenytoin, Phenobarbital, or Primidone and Not Taking Valproate**  
1531 **(Green ODT Kit)**

1532 50 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with “LMT”  
1533 on one side and “50” on the other, and 100 mg, white to off-white, round, flat-faced, radius edge,  
1534 tablets debossed with “LAMICTAL” on one side and “100” on the other, blisterpack of 56  
1535 tablets (42/50-mg tablets and 14/100-mg tablets) (NDC 0173-0780-00).

1536 **LAMICTAL ODT (lamotrigine) Patient Titration Kit for Patients Not Taking**  
1537 **Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate (Orange ODT Kit)**  
1538 25 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with “LMT”  
1539 on one side and “25” on the other, 50 mg, white to off-white, round, flat-faced, radius edge,  
1540 tablets debossed with “LMT” on one side and “50” on the other, and 100 mg, white to off-white,  
1541 round, flat-faced, radius edge, tablets debossed with “LAMICTAL” on one side and “100” on the  
1542 other, blisterpack of 35 (14/25-mg tablets, 14/50-mg tablets, and 7/100-mg tablets) (NDC 0173-  
1543 0778-00).

1544 Store between 20°C to 25°C (68°F to 77°F); with excursions permitted between 15°C and  
1545 30°C (59°F and 86°F).

1546 **Blisterpacks:** If the product is dispensed in a blisterpack, the patient should be advised to  
1547 examine the blisterpack before use and not use if blisters are torn, broken, or missing.

## 1548 **17 PATIENT COUNSELING INFORMATION**

1549 *See FDA-approved patient labeling (Medication Guide).*

### 1550 **17.1 Rash**

1551 Prior to initiation of treatment with LAMICTAL, the patient should be instructed that a  
1552 rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy) may herald a  
1553 serious medical event and that the patient should report any such occurrence to a physician  
1554 immediately.

### 1555 **17.2 Multiorgan Hypersensitivity Reactions, Blood Dyscrasias, and Organ Failure**

1557 Patients should be instructed that multiorgan hypersensitivity reactions and acute  
1558 multiorgan failure may occur with LAMICTAL. Isolated organ failure or isolated blood  
1559 dyscrasias without evidence of multiorgan hypersensitivity may also occur. Patients should  
1560 contact their physician immediately if they experience any signs or symptoms of these conditions  
1561 [see Warnings and Precautions (5.2, 5.3)].

### 1562 **17.3 Suicidal Thinking and Behavior**

1563 Patients, their caregivers, and families should be counseled that AEDs, including  
1564 LAMICTAL, may increase the risk of suicidal thoughts and behavior and should be advised of  
1565 the need to be alert for the emergence or worsening of symptoms of depression, any unusual  
1566 changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about  
1567 self-harm. Behaviors of concern should be reported immediately to healthcare providers.

### 1568 **17.4 Worsening of Seizures**

1569 Patients should be advised to notify their physician if worsening of seizure control  
1570 occurs.

### 1571 **17.5 Central Nervous System Adverse Effects**

1572 Patients should be advised that LAMICTAL may cause dizziness, somnolence, and other  
1573 symptoms and signs of CNS depression. Accordingly, they should be advised neither to drive a

1574 car nor to operate other complex machinery until they have gained sufficient experience on  
1575 LAMICTAL to gauge whether or not it adversely affects their mental and/or motor performance.

### 1576 **17.6 Pregnancy and Nursing**

1577 Patients should be advised to notify their physicians if they become pregnant or intend to  
1578 become pregnant during therapy. Patients should be advised to notify their physicians if they  
1579 intend to breastfeed or are breastfeeding an infant.

1580 Patients should also be encouraged to enroll in the NAAED Pregnancy Registry if they  
1581 become pregnant. This registry is collecting information about the safety of antiepileptic drugs  
1582 during pregnancy. To enroll, patients can call the toll-free number 1-888-233-2334 [*see Use in*  
1583 *Specific Populations (8.1)*].

1584 Patients who intend to breastfeed should be informed that LAMICTAL is present in  
1585 breast milk and that they should monitor their child for potential adverse effects of this drug.  
1586 Benefits and risks of continuing breastfeeding should be discussed with the patient.

### 1587 **17.7 Oral Contraceptive Use**

1588 Women should be advised to notify their physician if they plan to start or stop use of oral  
1589 contraceptives or other female hormonal preparations. Starting estrogen-containing oral  
1590 contraceptives may significantly decrease lamotrigine plasma levels and stopping estrogen-  
1591 containing oral contraceptives (including the “pill-free” week) may significantly increase  
1592 lamotrigine plasma levels [*see Warnings and Precautions (5.8), Clinical Pharmacology (12.3)*].  
1593 Women should also be advised to promptly notify their physician if they experience adverse  
1594 reactions or changes in menstrual pattern (e.g., break-through bleeding) while receiving  
1595 LAMICTAL in combination with these medications.

### 1596 **17.8 Discontinuing LAMICTAL**

1597 Patients should be advised to notify their physician if they stop taking LAMICTAL for  
1598 any reason and not to resume LAMICTAL without consulting their physician.

### 1599 **17.9 Aseptic Meningitis**

1600 Patients should be advised that LAMICTAL may cause aseptic meningitis. Patients  
1601 should be advised to notify their physician immediately if they develop signs and symptoms of  
1602 meningitis such as headache, fever, nausea, vomiting, stiff neck, rash, abnormal sensitivity to  
1603 light, myalgia, chills, confusion, or drowsiness while taking LAMICTAL.

### 1604 **17.10 Potential Medication Errors**

1605 Medication errors involving LAMICTAL have occurred. In particular the names  
1606 LAMICTAL or lamotrigine can be confused with the names of other commonly used  
1607 medications. Medication errors may also occur between the different formulations of  
1608 LAMICTAL. To reduce the potential of medication errors, write and say LAMICTAL clearly.  
1609 Depictions of the LAMICTAL Tablets, Chewable Dispersible Tablets, and Orally Disintegrating  
1610 Tablets can be found in the Medication Guide that accompanies the product to highlight the  
1611 distinctive markings, colors, and shapes that serve to identify the different presentations of the  
1612 drug and thus may help reduce the risk of medication errors. **To avoid a medication error of**

1613 **using the wrong drug or formulation, patients should be strongly advised to visually**  
1614 **inspect their tablets to verify that they are LAMICTAL, as well as the correct formulation**  
1615 **of LAMICTAL, each time they fill their prescription** [*see Dosage Forms and Strengths (3.1,*  
1616 *3.2, 3.3), How Supplied/Storage and Handling (16)*].

1617  
1618 LAMICTAL is a registered trademark of GlaxoSmithKline.  
1619 Microcaps and AdvaTab are registered trademarks of Eurand, Inc.

1620  
1621



1622  
1623 GlaxoSmithKline  
1624 Research Triangle Park, NC 27709

1625  
1626 LAMICTAL Tablets and Chewable Dispersible Tablets are manufactured by  
1627 DSM Pharmaceuticals, Inc., Greenville, NC 27834 or  
1628 GlaxoSmithKline, Research Triangle Park, NC 27709

1629  
1630 LAMICTAL Orally Disintegrating Tablets are manufactured by  
1631 Eurand, Inc., Vandalia, OH 45377

1632  
1633  
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1635  
1636 Month Year  
1637 LMT:xPI

1638

## 1639 MEDICATION GUIDE

1640

### 1641 **LAMICTAL<sup>®</sup> (la-MIK-tal) (lamotrigine) Tablets and Chewable Dispersible Tablets** 1642 **LAMICTAL<sup>®</sup> ODT<sup>™</sup> (lamotrigine) Orally Disintegrating Tablets**

1643

1644 Read this Medication Guide before you start taking LAMICTAL and each time you get a refill.  
1645 There may be new information. This information does not take the place of talking with your  
1646 healthcare provider about your medical condition or treatment. If you have questions about  
1647 LAMICTAL, ask your healthcare provider or pharmacist.

1648

1649 **What is the most important information I should know about LAMICTAL?**

1650 **1. LAMICTAL may cause a serious skin rash that may cause you to be hospitalized or to**  
1651 **stop LAMICTAL; it may rarely cause death.**

1652 There is no way to tell if a mild rash will develop into a more serious reaction. These serious  
1653 skin reactions are more likely to happen when you begin taking LAMICTAL, within the first  
1654 2 to 8 weeks of treatment. But it can happen in people who have taken LAMICTAL for any  
1655 period of time. Children between 2 to 16 years of age have a higher chance of getting this  
1656 serious skin reaction while taking LAMICTAL.

1657 The risk of getting a rash is higher if you:

- 1658 • take LAMICTAL while taking valproate [DEPAKENE (valproic acid) or DEPAKOTE
- 1659 (divalproex sodium)].
- 1660 • take a higher starting dose of LAMICTAL than your healthcare provider prescribed
- 1661 • increase your dose of LAMICTAL faster than prescribed.

1662 **LAMICTAL can also cause other types of allergic reactions or serious problems which**  
1663 **may affect organs and other parts of your body like the liver or blood cells. You may or**  
1664 **may not have a rash with these types of reactions.**

1665 **Call your healthcare provider right away if you have any of the following:**

- 1666 • a skin rash
- 1667 • hives
- 1668 • fever
- 1669 • swollen lymph glands
- 1670 • painful sores in the mouth or around your eyes
- 1671 • swelling of your lips or tongue
- 1672 • yellowing of your skin or eyes
- 1673 • unusual bruising or bleeding
- 1674 • severe fatigue or weakness
- 1675 • severe muscle pain
- 1676 • frequent infections

1677 These symptoms may be the first signs of a serious reaction. A healthcare provider should  
1678 examine you to decide if you should continue taking LAMICTAL.

1679 **2. Like other antiepileptic drugs, LAMICTAL may cause suicidal thoughts or actions in a**  
1680 **very small number of people, about 1 in 500.**

1681 **Call a healthcare provider right away if you have any of these symptoms, especially if**  
1682 **they are new, worse, or worry you:**

- 1683 • thoughts about suicide or dying
- 1684 • attempt to commit suicide
- 1685 • new or worse depression
- 1686 • new or worse anxiety

- 1687 • feeling agitated or restless
- 1688 • panic attacks
- 1689 • trouble sleeping (insomnia)
- 1690 • new or worse irritability
- 1691 • acting aggressive, being angry, or violent
- 1692 • acting on dangerous impulses
- 1693 • an extreme increase in activity and talking (mania)
- 1694 • other unusual changes in behavior or mood

1695 **Do not stop LAMICTAL without first talking to a healthcare provider.**

- 1696 • Stopping LAMICTAL suddenly can cause serious problems.
- 1697 • Suicidal thoughts or actions can be caused by things other than medicines. If you have
- 1698 suicidal thoughts or actions, your healthcare provider may check for other causes.

1699 **How can I watch for early symptoms of suicidal thoughts and actions?**

- 1700 • Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or
- 1701 feelings.
- 1702 • Keep all follow-up visits with your healthcare provider as scheduled.
- 1703 • Call your healthcare provider between visits as needed, especially if you are worried
- 1704 about symptoms.

1705 **3. LAMICTAL may rarely cause aseptic meningitis, a serious inflammation of the**

1706 **protective membrane that covers the brain and spinal cord.**

1707 **Call your healthcare provider right away if you have any of the following symptoms:**

- 1708 • Headache
- 1709 • Fever
- 1710 • Nausea
- 1711 • Vomiting
- 1712 • Stiff neck
- 1713 • Rash
- 1714 • Unusual sensitivity to light
- 1715 • Muscle pains
- 1716 • Chills
- 1717 • Confusion
- 1718 • Drowsiness

1719 Meningitis has many causes other than LAMICTAL, which your doctor would check for if

1720 you developed meningitis while taking LAMICTAL.

1721 **LAMICTAL can have other serious side effects.** For more information ask your healthcare

1722 provider or pharmacist. Tell your healthcare provider if you have any side effect that bothers

1723 you. Be sure to read the section below entitled “What are the possible side effects of  
 1724 LAMICTAL?”

1725 **4. Patients prescribed LAMICTAL have sometimes been given the wrong medicine**  
 1726 **because many medicines have names similar to LAMICTAL, so always check that you**  
 1727 **receive LAMICTAL.**

1728 Taking the wrong medication can cause serious health problems. When your healthcare  
 1729 provider gives you a prescription for LAMICTAL:

- 1730 • Make sure you can read it clearly.
- 1731 • Talk to your pharmacist to check that you are given the correct medicine.
- 1732 • Each time you fill your prescription, check the tablets you receive against the pictures of  
 1733 the tablets below.

1734 These pictures show the distinct wording, colors, and shapes of the tablets that help to  
 1735 identify the right strength of LAMICTAL Tablets, Chewable Dispersible Tablets, and  
 1736 Orally Disintegrating Tablets. Immediately call your pharmacist if you receive a  
 1737 LAMICTAL tablet that does not look like one of the tablets shown below, as you may  
 1738 have received the wrong medication.

1739 **LAMICTAL (lamotrigine) Tablets**

			
<b>25 mg, white</b>	<b>100 mg, peach</b>	<b>150 mg, cream</b>	<b>200 mg, blue</b>
<b>Imprinted with LAMICTAL 25</b>	<b>Imprinted with LAMICTAL 100</b>	<b>Imprinted with LAMICTAL 150</b>	<b>Imprinted with LAMICTAL 200</b>

1740 **LAMICTAL (lamotrigine) Chewable Dispersible Tablets**

		
<b>2 mg, white</b>	<b>5 mg, white</b>	<b>25 mg, white</b>
<b>Imprinted with LTG 2</b>	<b>Imprinted with GX CL2</b>	<b>Imprinted with GX CL5</b>

1741 **LAMICTAL ODT (lamotrigine) Orally Disintegrating Tablets**

			
<b>25 mg, white to off-white</b>	<b>50 mg, white to off-white</b>	<b>100 mg, white to off-white</b>	<b>200 mg, white to off-white</b>

<b>Imprinted with LMT on one side 25 on the other</b>	<b>Imprinted with LMT on one side 50 on the other</b>	<b>Imprinted with LAMICTAL on one side 100 on the other</b>	<b>Imprinted with LAMICTAL on one side 200 on the other</b>
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1742

1743 **What is LAMICTAL?**

1744 LAMICTAL is a prescription medicine used:

- 1745 1. together with other medicines to treat certain types of seizures (partial seizures, primary  
1746 generalized tonic-clonic seizures, generalized seizures of Lennox-Gastaut syndrome) in  
1747 people 2 years or older.
- 1748 2. alone when changing from other medicines used to treat partial seizures in people 16 years or  
1749 older.
- 1750 3. for the long-term treatment of Bipolar I Disorder to lengthen the time between mood  
1751 episodes in people 18 years or older who have been treated for mood episodes with other  
1752 medicine.

1753 It is not known if LAMICTAL is safe or effective in children or teenagers under the age of 18  
1754 with mood disorders such as bipolar disorder or depression.

1755 It is not known if LAMICTAL is safe or effective when used alone as the first treatment of  
1756 seizures in adults.

1757

1758 **Who should not take LAMICTAL?**

1759 You should not take LAMICTAL if you have had an allergic reaction to lamotrigine or to any of  
1760 the inactive ingredients in LAMICTAL. See the end of this leaflet for a complete list of  
1761 ingredients in LAMICTAL.

1762

1763 **What should I tell my healthcare provider before taking LAMICTAL?**

1764 Before taking LAMICTAL, tell your healthcare provider about all of your medical conditions,  
1765 including if you:

- 1766 • have had a rash or allergic reaction to another antiseizure medicine.
- 1767 • have or have had depression, mood problems or suicidal thoughts or behavior.
- 1768 • are taking oral contraceptives (birth control pills) or other female hormonal medicines. Do  
1769 not start or stop taking birth control pills or other female hormonal medicine until you have  
1770 talked with your healthcare provider. Tell your healthcare provider if you have any changes  
1771 in your menstrual pattern such as breakthrough bleeding. Stopping or starting these  
1772 medicines may cause side effects (such as dizziness, lack of coordination, or double vision)  
1773 or lessen how well LAMICTAL works.

1774 • are pregnant or plan to become pregnant. It is not known if LAMICTAL will harm your  
1775 unborn baby. If you become pregnant while taking LAMICTAL, talk to your healthcare  
1776 provider about registering with the North American Antiepileptic Drug Pregnancy Registry.  
1777 You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to  
1778 collect information about the safety of antiepileptic drugs during pregnancy.

1779 • are breastfeeding. LAMICTAL passes into breast milk and may cause side effects in a  
1780 breastfed baby. If you breastfeed while taking LAMICTAL, watch your baby closely for  
1781 trouble breathing, episodes of temporarily stopping breathing, sleepiness, or poor sucking.  
1782 Call your baby's healthcare provider right away if you see any of these problems. Talk to  
1783 your healthcare provider about the best way to feed your baby if you take LAMICTAL.

1784 Tell your healthcare provider about all the medicines you take or if you are planning to take a  
1785 new medicine, including prescription and non-prescription medicines, vitamins, and herbal  
1786 supplements. Using LAMICTAL with certain other medicines can affect each other, causing side  
1787 effects.

1788

#### 1789 **How should I take LAMICTAL?**

1790 • Take LAMICTAL exactly as prescribed.

1791 • Your healthcare provider may change your dose. Do not change your dose without talking to  
1792 your healthcare provider.

1793 • Do not stop taking LAMICTAL without talking to your healthcare provider. Stopping  
1794 LAMICTAL suddenly may cause serious problems. For example, if you have epilepsy and  
1795 you stop taking LAMICTAL suddenly, you may get seizures that do not stop. Talk with your  
1796 healthcare provider about how to stop LAMICTAL slowly.

1797 • If you miss a dose of LAMICTAL, take it as soon as you remember. If it is almost time for  
1798 your next dose, just skip the missed dose. Take the next dose at your regular time. **Do not**  
1799 **take two doses at the same time.**

1800 • If you take too much LAMICTAL, call your healthcare provider or your local Poison Control  
1801 Center or go to the nearest hospital emergency room right away.

1802 • You may not feel the full effect of LAMICTAL for several weeks.

1803 • If you have epilepsy, tell your healthcare provider if your seizures get worse or if you have  
1804 any new types of seizures.

1805 • Swallow LAMICTAL tablets whole.

1806 • If you have trouble swallowing LAMICTAL Tablets, there may be another form of  
1807 LAMICTAL you can take.

1808 • LAMICTAL ODT should be placed on the tongue and moved around the mouth. The tablet  
1809 will rapidly disintegrate, can be swallowed with or without water, and can be taken with or  
1810 without food.

1811 • LAMICTAL Chewable Dispersible tablets may be swallowed whole, chewed, or mixed in  
1812 water or diluted fruit juice. If the tablets are chewed, drink a small amount of water or diluted

1813 fruit juice to help in swallowing. To break up LAMICTAL Chewable Dispersible tablets, add  
1814 the tablets to a small amount of liquid (1 teaspoon, or enough to cover the medicine) in a  
1815 glass or spoon. Wait at least 1 minute or until the tablets are completely broken up, mix the  
1816 solution together and take the whole amount right away.

- 1817 • If you receive LAMICTAL in a blisterpack, examine the blisterpack before use. Do not use if  
1818 blisters are torn, broken, or missing.

1819

### 1820 **What should I avoid while taking LAMICTAL?**

- 1821 • Do not drive a car or operate complex, hazardous machinery until you know how  
1822 LAMICTAL affects you.

1823

### 1824 **What are possible side effects of LAMICTAL?**

- 1825 • See “What is the most important information I should know about LAMICTAL?”

1826 Common side effects of LAMICTAL include:

• dizziness	• tremor
• headache	• rash
• blurred or double vision	• fever
• lack of coordination	• abdominal pain
• sleepiness	• back pain
• nausea, vomiting	• tiredness
• insomnia	• dry mouth

1827 Tell your healthcare provider about any side effect that bothers you or that does not go away.

1828 These are not all the possible side effects of LAMICTAL. For more information, ask your  
1829 healthcare provider or pharmacist.

1830 Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-  
1831 800-FDA-1088.

1832

### 1833 **How should I store LAMICTAL?**

- 1834 • Store LAMICTAL at room temperature between 68°F to 77°F (20°C to 25°C).
- 1835 • **Keep LAMICTAL and all medicines out of the reach of children.**

1836

### 1837 **General information about LAMICTAL**

1838 Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.  
1839 Do not use LAMICTAL for a condition for which it was not prescribed. Do not give  
1840 LAMICTAL to other people, even if they have the same symptoms you have. It may harm them.  
1841 This Medication Guide summarizes the most important information about LAMICTAL. If you  
1842 would like more information, talk with your healthcare provider. You can ask your healthcare  
1843 provider or pharmacist for information about LAMICTAL that is written for healthcare  
1844 professionals.  
1845 For more information, go to [www.lamictal.com](http://www.lamictal.com) or call 1-888-825-5249.

1847 **What are the ingredients in LAMICTAL?**

1848 **LAMICTAL Tablets**

1849 Active ingredient: lamotrigine.

1850 Inactive ingredients: lactose; magnesium stearate, microcrystalline cellulose, povidone, sodium  
1851 starch glycolate, FD&C Yellow No. 6 Lake (100-mg tablet only), ferric oxide, yellow (150-mg  
1852 tablet only), and FD&C Blue No. 2 Lake (200-mg tablet only).

1853 **LAMICTAL Chewable Dispersible Tablets**

1854 Active ingredient: lamotrigine.

1855 Inactive ingredients: blackcurrant flavor, calcium carbonate, low-substituted  
1856 hydroxypropylcellulose, magnesium aluminum silicate, magnesium stearate, povidone, saccharin  
1857 sodium, and sodium starch glycolate.

1858 **LAMICTAL ODT Orally Disintegrating Tablets**

1859 Active ingredient: lamotrigine.

1860 Inactive ingredients: artificial cherry flavor, crospovidone, ethylcellulose, magnesium stearate,  
1861 mannitol, polyethylene, and sucralose.

1862

1863 **This Medication Guide has been approved by the U.S. Food and Drug Administration.**

1864

1865 LAMICTAL is a registered trademark of GlaxoSmithKline.

1866 DEPAKENE and DEPAKOTE are registered trademarks of Abbott Laboratories.

1867

1868



1869

1870 GlaxoSmithKline

1871 Research Triangle Park, NC 27709

1872

1873 LAMICTAL Tablets and Chewable Dispersible Tablets are manufactured by  
1874 DSM Pharmaceuticals, Inc.,  
1875 Greenville, NC 27834 or  
1876 GlaxoSmithKline  
1877 Research Triangle Park, NC 27709  
1878  
1879 LAMICTAL Orally Disintegrating Tablets are manufactured by  
1880 Eurand, Inc., Vandalia, OH 45377  
1881  
1882 ©Year, GlaxoSmithKline. All rights reserved.  
1883  
1884 Month Year  
1885 LMT:xMG