

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 1

### 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) July 2011  
Warnings and Precautions, Aseptic Meningitis (5.6) October 2010

#### INDICATIONS AND USAGE

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

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

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

#### DOSAGE AND ADMINISTRATION

- Dosing is based on concomitant medications, indication, and patient age. (2.2, 2.4)
- To avoid an increased risk of rash, the recommended initial dose and subsequent dose escalations should not be exceeded. LAMICTAL Starter Kits and LAMICTAL ODT Patient Titration Kits are available for the first 5 weeks of treatment. (2.1, 16)
- Do not restart LAMICTAL in patients who discontinued due to rash unless the potential benefits clearly outweigh the risks. (2.1)
- Adjustments to maintenance doses will in most cases be required in patients starting or stopping estrogen-containing oral contraceptives. (2.1, 5.8)
- 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 ≥10%) in adult epilepsy clinical studies were dizziness, headache, diplopia, ataxia, nausea, blurred vision, somnolence, rhinitis, and rash. Additional adverse reactions (incidence ≥10%) reported in children in epilepsy clinical studies included vomiting, infection, fever, accidental injury, pharyngitis, abdominal pain, and tremor. (6.1)
- Most common adverse reactions (incidence >5%) in adult bipolar clinical studies were nausea, insomnia, somnolence, back pain, fatigue, rash, rhinitis, abdominal pain, and xerostomia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](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: 07/2011

## 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

NDA 020241/S-047

NDA 020764/S-040

NDA 022251/S-010

FDA Approved Labeling Text dated 7/28/2011

Page 2

- 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 CNS Adverse Effects
  - 17.6 Pregnancy
  - 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.

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 3

## 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

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 4

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

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 5

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

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 6

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

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 7

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

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 8

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 which 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

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 9

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

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 10

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 which 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 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**

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 11

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

## 259 **2.4 Bipolar Disorder**

260 The goal of maintenance treatment with LAMICTAL is to delay the time to occurrence of  
261 mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute  
262 mood episodes with standard therapy. The target dose of LAMICTAL is 200 mg/day (100

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 12

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

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

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

283  
284

**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

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 13

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

295 **Table 6. Dosage Adjustments to LAMICTAL for Patients With Bipolar Disorder Following**  
296 **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

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

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

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 14

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

## 312 **2.5 Administration of LAMICTAL Chewable Dispersible Tablets**

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

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

## 320 **2.6 Administration of LAMICTAL ODT Orally Disintegrating Tablets**

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

## 324 **3 DOSAGE FORMS AND STRENGTHS**

### 325 **3.1 Tablets**

326 25 mg, white, scored, shield-shaped tablets debossed with “LAMICTAL” and “25”  
327 100 mg, peach, scored, shield-shaped tablets debossed with “LAMICTAL” and “100”  
328 150 mg, cream, scored, shield-shaped tablets debossed with “LAMICTAL” and “150”  
329 200 mg, blue, scored, shield-shaped tablets debossed with “LAMICTAL” and “200”

### 330 **3.2 Chewable Dispersible Tablets**

331 2 mg, white to off-white, round tablets debossed with “LTG” over “2”  
332 5 mg, white to off-white, caplet-shaped tablets debossed with “GX CL2”  
333 25 mg, white, super elliptical-shaped tablets debossed with “GX CL5”

### 334 **3.3 Orally Disintegrating Tablets**

335 25 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with “LMT”  
336 on one side and “25” on the other side.

337 50 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with “LMT”  
338 on one side and “50” on the other side.

339 100 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with  
340 “LAMICTAL” on one side and “100” on the other side.

341 200 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with  
342 “LAMICTAL” on one side and “200” on the other side.

### 343 **3.4 Potential Medication Errors**

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

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 15

348 **4 CONTRAINDICATIONS**

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

351 **5 WARNINGS AND PRECAUTIONS**

352 **5.1 Serious Skin Rashes [*see Boxed Warning*]**

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

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

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

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

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

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

385 **5.2 Multiorgan Hypersensitivity Reactions and Organ Failure**

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 16

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

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

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

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

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

### 407 **5.3 Blood Dyscrasias**

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

### 412 **5.4 Suicidal Behavior and Ideation**

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

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

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 17

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

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

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

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

436

437 **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

438

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

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

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

## 453 **5.5 Use in Patients With Bipolar Disorder**

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 18

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

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

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

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

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

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

## 477 **5.6 Aseptic Meningitis**

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

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

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

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 19

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

### 499 **5.7 Potential Medication Errors**

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

### 511 **5.8 Concomitant Use With Oral Contraceptives**

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

### 519 **5.9 Withdrawal Seizures**

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

### 527 **5.10 Status Epilepticus**

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

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 20

532 reports of variably defined episodes of seizure exacerbation (e.g., seizure clusters, seizure  
533 flurries, etc.) were made.

### 534 **5.11 Sudden Unexplained Death in Epilepsy (SUDEP)**

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

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

### 552 **5.12 Addition of LAMICTAL to a Multidrug Regimen That Includes Valproate**

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

### 555 **5.13 Binding in the Eye and Other Melanin-Containing Tissues**

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

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

### 565 **5.14 Laboratory Tests**

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

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 21

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

## 572 **6 ADVERSE REACTIONS**

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

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

### 583 **6.1 Clinical Trials**

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

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

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

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

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

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 22

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

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

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

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

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

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

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 23

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

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 24

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

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

651

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

655

656 **Table 9. Dose-Related Adverse Reactions From a Randomized, Placebo-Controlled**  
657 **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>

658 <sup>a</sup> Significantly greater than placebo group ( $p < 0.05$ ).

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

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 25

660

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

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

676

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

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 26

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

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

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

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

686

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

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

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

691 *Metabolic and Nutritional:* Peripheral edema.

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

694 *Respiratory:* Epistaxis, bronchitis, dyspnea.

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

696 *Special Senses:* Vision abnormality.

697 *Incidence in Controlled Adjunctive Trials in Pediatric Patients With*

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

702

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 27

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

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 28

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

707

708

709

710

711

712

713

714

715

716

**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%).

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 29

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

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

728

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

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

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 30

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

737 <sup>b</sup> In the overall bipolar and other mood disorders clinical trials, the rate of serious rash was 0.08%  
738 (1 of 1,233) of adult patients who received LAMICTAL as initial monotherapy and 0.13% (2 of  
739 1,538) of adult patients who received LAMICTAL as adjunctive therapy [*see Warnings and*  
740 *Precautions (5.1)*].

741  
742 These adverse reactions were usually mild to moderate in intensity. Other reactions that  
743 occurred in 5% or more patients but equally or more frequently in the placebo group included:  
744 dizziness, mania, headache, infection, influenza, pain, accidental injury, diarrhea, and dyspepsia.

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

747 *General:* Fever, neck pain.

748 *Cardiovascular:* Migraine.

749 *Digestive:* Flatulence.

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

751 *Musculoskeletal:* Arthralgia, myalgia.

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

754 *Respiratory:* Sinusitis.

755 *Urogenital:* Urinary frequency.

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

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

## 771 **6.2 Other Adverse Reactions Observed in All Clinical Trials**

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

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 31

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

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

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

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

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

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

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

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

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

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

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

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 32

813 dystonia, extrapyramidal syndrome, faintness, grand mal convulsions, hemiplegia, hyperalgesia,  
814 hyperesthesia, hypokinesia, hypotonia, manic depression reaction, muscle spasm, neuralgia,  
815 neurosis, paralysis, and peripheral neuritis.

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

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

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

### 825 **6.3 Postmarketing Experience**

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

830 Blood and Lymphatic: Agranulocytosis, hemolytic anemia.

831 Gastrointestinal: Esophagitis.

832 Hepatobiliary Tract and Pancreas: Pancreatitis.

833 Immunologic: Lupus-like reaction, vasculitis.

834 Lower Respiratory: Apnea.

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

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

839 Non-site Specific: Progressive immunosuppression.

## 840 **7 DRUG INTERACTIONS**

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

844

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

Concomitant Drug	Effect on Concentration of Lamotrigine or Concomitant Drug	Clinical Comment
Estrogen-containing oral contraceptive	↓ lamotrigine	Decreased lamotrigine levels approximately 50%.

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 33

preparations containing 30 mcg ethinylestradiol and 150 mcg levonorgestrel	↓ levonorgestrel	Decrease in levonorgestrel component by 19%.
Carbamazepine (CBZ) and CBZ epoxide	↓ lamotrigine ? CBZ epoxide	Addition of carbamazepine decreases lamotrigine concentration approximately 40%. May increase CBZ epoxide levels.
Phenobarbital/Primidone	↓ lamotrigine	Decreased lamotrigine concentration approximately 40%.
Phenytoin (PHT)	↓ lamotrigine	Decreased lamotrigine concentration approximately 40%.
Rifampin	↓ lamotrigine	Decreased lamotrigine AUC approximately 40%.
Valproate	↑ lamotrigine ? valproate	Increased lamotrigine concentrations slightly more than 2-fold. Decreased valproate concentrations an average of 25% over a 3-week period then stabilized in healthy volunteers; no change in controlled clinical trials in epilepsy patients.

846 ↓ = Decreased (induces lamotrigine glucuronidation).

847 ↑ = Increased (inhibits lamotrigine glucuronidation).

848 ? = Conflicting data.

849 **8 USE IN SPECIFIC POPULATIONS**

850 **8.1 Pregnancy**

851 Teratogenic Effects: Pregnancy Category C. No evidence of teratogenicity was found in  
852 mice, rats, or rabbits when lamotrigine was orally administered to pregnant animals during the  
853 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  
854 highest usual human maintenance dose (i.e., 500 mg/day). However, maternal toxicity and  
855 secondary fetal toxicity producing reduced fetal weight and/or delayed ossification were seen in  
856 mice and rats, but not in rabbits at these doses. Teratology studies were also conducted using  
857 bolus intravenous administration of the isethionate salt of lamotrigine in rats and rabbits. In rat  
858 dams administered an intravenous dose at 0.6 times the highest usual human maintenance dose,  
859 the incidence of intrauterine death without signs of teratogenicity was increased.

860 A behavioral teratology study was conducted in rats dosed during the period of  
861 organogenesis. At day 21 postpartum, offspring of dams receiving 5 mg/kg/day or higher  
862 displayed a significantly longer latent period for open field exploration and a lower frequency of

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 34

863 rearing. In a swimming maze test performed on days 39 to 44 postpartum, time to completion  
864 was increased in offspring of dams receiving 25 mg/kg/day. These doses represent 0.1 and 0.5  
865 times the clinical dose on a mg/m<sup>2</sup> basis, respectively.

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

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

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

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

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

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

## 898 **8.2 Labor and Delivery**

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

## 900 **8.3 Nursing Mothers**

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 35

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

#### 904 **8.4 Pediatric Use**

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

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

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

#### 918 **8.5 Geriatric Use**

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

#### 925 **8.6 Patients With Hepatic Impairment**

926 Experience in patients with hepatic impairment is limited. Based on a clinical  
927 pharmacology study in 24 patients with mild, moderate, and severe liver impairment [*see*  
928 *Clinical Pharmacology (12.3)*], the following general recommendations can be made. No dosage  
929 adjustment is needed in patients with mild liver impairment. Initial, escalation, and maintenance  
930 doses should generally be reduced by approximately 25% in patients with moderate and severe  
931 liver impairment without ascites and 50% in patients with severe liver impairment with ascites.  
932 Escalation and maintenance doses may be adjusted according to clinical response [*see Dosage*  
933 *and Administration (2.1)*].

#### 934 **8.7 Patients With Renal Impairment**

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

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 36

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

## 945 **10 OVERDOSAGE**

### 946 **10.1 Human Overdose Experience**

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

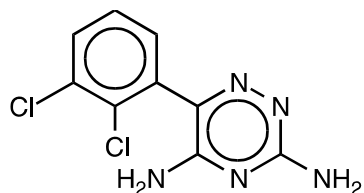
### 950 **10.2 Management of Overdose**

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

## 960 **11 DESCRIPTION**

961 LAMICTAL (lamotrigine), an AED of the phenyltriazine class, is chemically unrelated to  
962 existing AEDs. Its chemical name is 3,5-diamino-6-(2,3-dichlorophenyl)-*as*-triazine, its  
963 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  
964 pale cream-colored powder and has a pK<sub>a</sub> of 5.7. Lamotrigine is very slightly soluble in water  
965 (0.17 mg/mL at 25°C) and slightly soluble in 0.1 M HCl (4.1 mg/mL at 25°C). The structural  
966 formula is:

967



968

969

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

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 37

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

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

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

## 989 **12 CLINICAL PHARMACOLOGY**

### 990 **12.1 Mechanism of Action**

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

998 One proposed mechanism of action of lamotrigine, the relevance of which remains to be  
999 established in humans, involves an effect on sodium channels. In vitro pharmacological studies  
1000 suggest that lamotrigine inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal  
1001 membranes and consequently modulating presynaptic transmitter release of excitatory amino  
1002 acids (e.g., glutamate and aspartate).

1003 Although the relevance for human use is unknown, the following data characterize the  
1004 performance of lamotrigine in receptor binding assays. Lamotrigine had a weak inhibitory effect  
1005 on the serotonin 5-HT<sub>3</sub> receptor (IC<sub>50</sub> = 18 μM). It does not exhibit high affinity binding  
1006 (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>,  
1007 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  
1008 opioid; muscarinic acetylcholine; and serotonin 5-HT<sub>2</sub>. Studies have failed to detect an effect of  
1009 lamotrigine on dihydropyridine-sensitive calcium channels. It had weak effects at sigma opioid  
1010 receptors (IC<sub>50</sub> = 145 μM). Lamotrigine did not inhibit the uptake of norepinephrine, dopamine,  
1011 or serotonin (IC<sub>50</sub>>200 μM) when tested in rat synaptosomes and/or human platelets in vitro.

#### 1012 Effect of Lamotrigine on N-Methyl d-Aspartate-Receptor Mediated Activity:

1013 Lamotrigine did not inhibit N-methyl d-aspartate (NMDA)-induced depolarizations in rat cortical

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 38

1014 slices or NMDA-induced cyclic GMP formation in immature rat cerebellum, nor did lamotrigine  
1015 displace compounds that are either competitive or noncompetitive ligands at this glutamate  
1016 receptor complex (CNQX, CGS, TCHP). The IC<sub>50</sub> for lamotrigine effects on NMDA-induced  
1017 currents (in the presence of 3 μM of glycine) in cultured hippocampal neurons exceeded 100  
1018 μM.

1019 The mechanisms by which lamotrigine exerts its therapeutic action in Bipolar Disorder  
1020 have not been established.

## 1021 **12.2 Pharmacodynamics**

1022 Folate Metabolism: In vitro, lamotrigine inhibited dihydrofolate reductase, the enzyme  
1023 that catalyzes the reduction of dihydrofolate to tetrahydrofolate. Inhibition of this enzyme may  
1024 interfere with the biosynthesis of nucleic acids and proteins. When oral daily doses of  
1025 lamotrigine were given to pregnant rats during organogenesis, fetal, placental, and maternal  
1026 folate concentrations were reduced. Significantly reduced concentrations of folate are associated  
1027 with teratogenesis [see *Use in Specific Populations (8.1)*]. Folate concentrations were also  
1028 reduced in male rats given repeated oral doses of lamotrigine. Reduced concentrations were  
1029 partially returned to normal when supplemented with folic acid.

1030 Accumulation in Kidneys: Lamotrigine accumulated in the kidney of the male rat,  
1031 causing chronic progressive nephrosis, necrosis, and mineralization. These findings are attributed  
1032 to α-2 microglobulin, a species- and sex-specific protein that has not been detected in humans or  
1033 other animal species.

1034 Melanin Binding: Lamotrigine binds to melanin-containing tissues, e.g., in the eye and  
1035 pigmented skin. It has been found in the uveal tract up to 52 weeks after a single dose in rodents.

1036 Cardiovascular: In dogs, lamotrigine is extensively metabolized to a 2-N-methyl  
1037 metabolite. This metabolite causes dose-dependent prolongations of the PR interval, widening of  
1038 the QRS complex, and, at higher doses, complete AV conduction block. Similar cardiovascular  
1039 effects are not anticipated in humans because only trace amounts of the 2-N-methyl metabolite  
1040 (<0.6% of lamotrigine dose) have been found in human urine [see *Clinical Pharmacology*  
1041 *(12.3)*]. However, it is conceivable that plasma concentrations of this metabolite could be  
1042 increased in patients with a reduced capacity to glucuronidate lamotrigine (e.g., in patients with  
1043 liver disease).

## 1044 **12.3 Pharmacokinetics**

1045 The pharmacokinetics of lamotrigine have been studied in patients with epilepsy, healthy  
1046 young and elderly volunteers, and volunteers with chronic renal failure. Lamotrigine  
1047 pharmacokinetic parameters for adult and pediatric patients and healthy normal volunteers are  
1048 summarized in Tables 14 and 16.

1049

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 39

1050 **Table 14. Mean<sup>a</sup> Pharmacokinetic Parameters in Healthy Volunteers and Adult Patients**  
1051 **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)

1052 <sup>a</sup> The majority of parameter means determined in each study had coefficients of variation  
1053 between 20% and 40% for half-life and Cl/F and between 30% and 70% for T<sub>max</sub>. The overall  
1054 mean values were calculated from individual study means that were weighted based on the

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 40

1055 number of volunteers/patients in each study. The numbers in parentheses below each  
1056 parameter mean represent the range of individual volunteer/patient values across studies.  
1057 <sup>b</sup> Carbamazepine, phenobarbital, phenytoin, and primidone have been shown to increase the  
1058 apparent clearance of lamotrigine. Estrogen-containing oral contraceptives and other drugs  
1059 such as rifampin that induce lamotrigine glucuronidation have also been shown to increase the  
1060 apparent clearance of lamotrigine [*see Drug Interactions (7)*].  
1061

1062 **Absorption:** Lamotrigine is rapidly and completely absorbed after oral administration  
1063 with negligible first-pass metabolism (absolute bioavailability is 98%). The bioavailability is not  
1064 affected by food. Peak plasma concentrations occur anywhere from 1.4 to 4.8 hours following  
1065 drug administration. The lamotrigine chewable/dispersible tablets were found to be equivalent,  
1066 whether they were administered as dispersed in water, chewed and swallowed, or swallowed as  
1067 whole, to the lamotrigine compressed tablets in terms of rate and extent of absorption. In terms  
1068 of rate and extent of absorption, lamotrigine orally disintegrating tablets whether disintegrated in  
1069 the mouth or swallowed whole with water were equivalent to the lamotrigine compressed tablets  
1070 swallowed with water.

1071 **Dose Proportionality:** In healthy volunteers not receiving any other medications and  
1072 given single doses, the plasma concentrations of lamotrigine increased in direct proportion to the  
1073 dose administered over the range of 50 to 400 mg. In 2 small studies (n = 7 and 8) of patients  
1074 with epilepsy who were maintained on other AEDs, there also was a linear relationship between  
1075 dose and lamotrigine plasma concentrations at steady state following doses of 50 to 350 mg  
1076 twice daily.

1077 **Distribution:** Estimates of the mean apparent volume of distribution (Vd/F) of  
1078 lamotrigine following oral administration ranged from 0.9 to 1.3 L/kg. Vd/F is independent of  
1079 dose and is similar following single and multiple doses in both patients with epilepsy and in  
1080 healthy volunteers.

1081 **Protein Binding:** Data from in vitro studies indicate that lamotrigine is approximately  
1082 55% bound to human plasma proteins at plasma lamotrigine concentrations from 1 to 10 mcg/mL  
1083 (10 mcg/mL is 4 to 6 times the trough plasma concentration observed in the controlled efficacy  
1084 trials). Because lamotrigine is not highly bound to plasma proteins, clinically significant  
1085 interactions with other drugs through competition for protein binding sites are unlikely. The  
1086 binding of lamotrigine to plasma proteins did not change in the presence of therapeutic  
1087 concentrations of phenytoin, phenobarbital, or valproate. Lamotrigine did not displace other  
1088 AEDs (carbamazepine, phenytoin, phenobarbital) from protein-binding sites.

1089 **Metabolism:** Lamotrigine is metabolized predominantly by glucuronic acid conjugation;  
1090 the major metabolite is an inactive 2-N-glucuronide conjugate. After oral administration of 240  
1091 mg of <sup>14</sup>C-lamotrigine (15 μCi) to 6 healthy volunteers, 94% was recovered in the urine and 2%  
1092 was recovered in the feces. The radioactivity in the urine consisted of unchanged lamotrigine

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 41

1093 (10%), the 2-N-glucuronide (76%), a 5-N-glucuronide (10%), a 2-N-methyl metabolite (0.14%),  
1094 and other unidentified minor metabolites (4%).

1095 **Enzyme Induction:** The effects of lamotrigine on the induction of specific families of  
1096 mixed-function oxidase isozymes have not been systematically evaluated.

1097 Following multiple administrations (150 mg twice daily) to normal volunteers taking no  
1098 other medications, lamotrigine induced its own metabolism, resulting in a 25% decrease in  $t_{1/2}$  and  
1099 a 37% increase in Cl/F at steady state compared with values obtained in the same volunteers  
1100 following a single dose. Evidence gathered from other sources suggests that self-induction by  
1101 lamotrigine may not occur when lamotrigine is given as adjunctive therapy in patients receiving  
1102 enzyme-inducing drugs such as carbamazepine, phenytoin, phenobarbital, primidone, or drugs  
1103 such as rifampin that induce lamotrigine glucuronidation [*see Drug Interactions (7)*].

1104 **Elimination:** The elimination half-life and apparent clearance of lamotrigine following  
1105 administration of LAMICTAL to adult patients with epilepsy and healthy volunteers is  
1106 summarized in Table 14. Half-life and apparent oral clearance vary depending on concomitant  
1107 AEDs.

1108 **Drug Interactions:** The apparent clearance of lamotrigine is affected by the  
1109 coadministration of certain medications [*see Warnings and Precautions (5.8, 5.13), Drug*  
1110 *Interactions (7)*].

1111 The net effects of drug interactions with LAMICTAL are summarized in Tables 13 and  
1112 15, followed by details of the drug interaction studies below.

1113

1114 **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	↔	↓

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 42

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

- 1115 <sup>a</sup> From adjunctive clinical trials and volunteer studies.
- 1116 <sup>b</sup> Net effects were estimated by comparing the mean clearance values obtained in adjunctive  
1117 clinical trials and volunteer studies.
- 1118 <sup>c</sup> The effect of other hormonal contraceptive preparations or hormone replacement therapy on  
1119 the pharmacokinetics of lamotrigine has not been systematically evaluated in clinical trials,  
1120 although the effect may be similar to that seen with the ethinylestradiol/levonorgestrel  
1121 combinations.
- 1122 <sup>d</sup> Modest decrease in levonorgestrel.
- 1123 <sup>e</sup> Not administered, but an active metabolite of carbamazepine.
- 1124 <sup>f</sup> Slight decrease, not expected to be clinically relevant.
- 1125 <sup>g</sup> Not administered, but an active metabolite of oxcarbazepine.
- 1126 <sup>h</sup> Slight increase, not expected to be clinically relevant.
- 1127 ↔ = No significant effect.
- 1128 ? = Conflicting data.
- 1129

1130 **Estrogen-Containing Oral Contraceptives:** In 16 female volunteers, an oral  
1131 contraceptive preparation containing 30 mcg ethinylestradiol and 150 mcg levonorgestrel  
1132 increased the apparent clearance of lamotrigine (300 mg/day) by approximately 2-fold with mean  
1133 decreases in AUC of 52% and in C<sub>max</sub> of 39%. In this study, trough serum lamotrigine  
1134 concentrations gradually increased and were approximately 2-fold higher on average at the end  
1135 of the week of the inactive hormone preparation compared with trough lamotrigine  
1136 concentrations at the end of the active hormone cycle.

1137 Gradual transient increases in lamotrigine plasma levels (approximate 2-fold increase)  
1138 occurred during the week of inactive hormone preparation (“pill-free” week) for women not also  
1139 taking a drug that increased the clearance of lamotrigine (carbamazepine, phenytoin,  
1140 phenobarbital, primidone, or other drugs such as rifampin that induce lamotrigine  
1141 glucuronidation [see *Drug Interactions (7)*]). The increase in lamotrigine plasma levels will be  
1142 greater if the dose of LAMICTAL is increased in the few days before or during the “pill-free”  
1143 week. Increases in lamotrigine plasma levels could result in dose-dependent adverse reactions.

1144 In the same study, coadministration of LAMICTAL (300 mg/day) in 16 female  
1145 volunteers did not affect the pharmacokinetics of the ethinylestradiol component of the oral  
1146 contraceptive preparation. There were mean decreases in the AUC and C<sub>max</sub> of the levonorgestrel

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 43

1147 component of 19% and 12%, respectively. Measurement of serum progesterone indicated that  
1148 there was no hormonal evidence of ovulation in any of the 16 volunteers, although measurement  
1149 of serum FSH, LH, and estradiol indicated that there was some loss of suppression of the  
1150 hypothalamic-pituitary-ovarian axis.

1151 The effects of doses of LAMICTAL other than 300 mg/day have not been systematically  
1152 evaluated in controlled clinical trials.

1153 The clinical significance of the observed hormonal changes on ovulatory activity is  
1154 unknown. However, the possibility of decreased contraceptive efficacy in some patients cannot  
1155 be excluded. Therefore, patients should be instructed to promptly report changes in their  
1156 menstrual pattern (e.g., break-through bleeding).

1157 Dosage adjustments may be necessary for women receiving estrogen-containing oral  
1158 contraceptive preparations [*see Dosage and Administration (2.1)*].

1159 **Other Hormonal Contraceptives or Hormone Replacement Therapy:** The effect of  
1160 other hormonal contraceptive preparations or hormone replacement therapy on the  
1161 pharmacokinetics of lamotrigine has not been systematically evaluated. It has been reported that  
1162 ethinylestradiol, not progestogens, increased the clearance of lamotrigine up to 2-fold, and the  
1163 progestin-only pills had no effect on lamotrigine plasma levels. Therefore, adjustments to the  
1164 dosage of LAMICTAL in the presence of progestogens alone will likely not be needed.

1165 **Bupropion:** The pharmacokinetics of a 100-mg single dose of LAMICTAL in healthy  
1166 volunteers (n = 12) were not changed by coadministration of bupropion sustained-release  
1167 formulation (150 mg twice daily) starting 11 days before LAMICTAL.

1168 **Carbamazepine:** LAMICTAL has no appreciable effect on steady-state carbamazepine  
1169 plasma concentration. Limited clinical data suggest there is a higher incidence of dizziness,  
1170 diplopia, ataxia, and blurred vision in patients receiving carbamazepine with lamotrigine than in  
1171 patients receiving other AEDs with lamotrigine [*see Adverse Reactions (6.1)*]. The mechanism  
1172 of this interaction is unclear. The effect of lamotrigine on plasma concentrations of  
1173 carbamazepine-epoxide is unclear. In a small subset of patients (n = 7) studied in a placebo-  
1174 controlled trial, lamotrigine had no effect on carbamazepine-epoxide plasma concentrations, but  
1175 in a small, uncontrolled study (n = 9), carbamazepine-epoxide levels increased.

1176 The addition of carbamazepine decreases lamotrigine steady-state concentrations by  
1177 approximately 40%.

1178 **Felbamate:** In a study of 21 healthy volunteers, coadministration of felbamate (1,200 mg  
1179 twice daily) with lamotrigine (100 mg twice daily for 10 days) appeared to have no clinically  
1180 relevant effects on the pharmacokinetics of lamotrigine.

1181 **Folate Inhibitors:** Lamotrigine is a weak inhibitor of dihydrofolate reductase. Prescribers  
1182 should be aware of this action when prescribing other medications that inhibit folate metabolism.

1183 **Gabapentin:** Based on a retrospective analysis of plasma levels in 34 patients who  
1184 received lamotrigine both with and without gabapentin, gabapentin does not appear to change the  
1185 apparent clearance of lamotrigine.

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 44

1186 Levetiracetam: Potential drug interactions between levetiracetam and lamotrigine were  
1187 assessed by evaluating serum concentrations of both agents during placebo-controlled clinical  
1188 trials. These data indicate that lamotrigine does not influence the pharmacokinetics of  
1189 levetiracetam and that levetiracetam does not influence the pharmacokinetics of lamotrigine.

1190 Lithium: The pharmacokinetics of lithium were not altered in healthy subjects (n = 20) by  
1191 coadministration of lamotrigine (100 mg/day) for 6 days.

1192 Olanzapine: The AUC and  $C_{max}$  of olanzapine were similar following the addition of  
1193 olanzapine (15 mg once daily) to lamotrigine (200 mg once daily) in healthy male volunteers (n  
1194 = 16) compared with the AUC and  $C_{max}$  in healthy male volunteers receiving olanzapine alone (n  
1195 = 16).

1196 In the same study, the AUC and  $C_{max}$  of lamotrigine were reduced on average by 24%  
1197 and 20%, respectively, following the addition of olanzapine to lamotrigine in healthy male  
1198 volunteers compared with those receiving lamotrigine alone. This reduction in lamotrigine  
1199 plasma concentrations is not expected to be clinically relevant.

1200 Oxcarbazepine: The AUC and  $C_{max}$  of oxcarbazepine and its active 10-monohydroxy  
1201 oxcarbazepine metabolite were not significantly different following the addition of  
1202 oxcarbazepine (600 mg twice daily) to lamotrigine (200 mg once daily) in healthy male  
1203 volunteers (n = 13) compared with healthy male volunteers receiving oxcarbazepine alone (n =  
1204 13).

1205 In the same study, the AUC and  $C_{max}$  of lamotrigine were similar following the addition  
1206 of oxcarbazepine (600 mg twice daily) to LAMICTAL in healthy male volunteers compared with  
1207 those receiving LAMICTAL alone. Limited clinical data suggest a higher incidence of headache,  
1208 dizziness, nausea, and somnolence with coadministration of lamotrigine and oxcarbazepine  
1209 compared with lamotrigine alone or oxcarbazepine alone.

1210 Phenobarbital, Primidone: The addition of phenobarbital or primidone decreases  
1211 lamotrigine steady-state concentrations by approximately 40%.

1212 Phenytoin: Lamotrigine has no appreciable effect on steady-state phenytoin plasma  
1213 concentrations in patients with epilepsy. The addition of phenytoin decreases lamotrigine steady-  
1214 state concentrations by approximately 40%.

1215 Pregabalin: Steady-state trough plasma concentrations of lamotrigine were not affected  
1216 by concomitant pregabalin (200 mg 3 times daily) administration. There are no pharmacokinetic  
1217 interactions between lamotrigine and pregabalin.

1218 Rifampin: In 10 male volunteers, rifampin (600 mg/day for 5 days) significantly  
1219 increased the apparent clearance of a single 25-mg dose of lamotrigine by approximately 2-fold  
1220 (AUC decreased by approximately 40%).

1221 Topiramate: Topiramate resulted in no change in plasma concentrations of lamotrigine.  
1222 Administration of lamotrigine resulted in a 15% increase in topiramate concentrations.

1223 Valproate: When lamotrigine was administered to healthy volunteers (n = 18) receiving  
1224 valproate, the trough steady-state valproate plasma concentrations decreased by an average of

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 45

1225 25% over a 3-week period, and then stabilized. However, adding lamotrigine to the existing  
1226 therapy did not cause a change in valproate plasma concentrations in either adult or pediatric  
1227 patients in controlled clinical trials.

1228 The addition of valproate increased lamotrigine steady-state concentrations in normal  
1229 volunteers by slightly more than 2-fold. In one study, maximal inhibition of lamotrigine  
1230 clearance was reached at valproate doses between 250 and 500 mg/day and did not increase as  
1231 the valproate dose was further increased.

1232 Zonisamide: In a study of 18 patients with epilepsy, coadministration of zonisamide  
1233 (200 to 400 mg/day) with lamotrigine (150 to 500 mg/day for 35 days) had no significant effect  
1234 on the pharmacokinetics of lamotrigine.

1235 Known Inducers or Inhibitors of Glucuronidation: Drugs other than those listed above  
1236 have not been systematically evaluated in combination with lamotrigine. Since lamotrigine is  
1237 metabolized predominately by glucuronic acid conjugation, drugs that are known to induce or  
1238 inhibit glucuronidation may affect the apparent clearance of lamotrigine and doses of lamotrigine  
1239 may require adjustment based on clinical response.

1240 Other: Results of in vitro experiments suggest that clearance of lamotrigine is unlikely to  
1241 be reduced by concomitant administration of amitriptyline, clonazepam, clozapine, fluoxetine,  
1242 haloperidol, lorazepam, phenelzine, risperidone, sertraline, or trazodone.

1243 Results of in vitro experiments suggest that lamotrigine does not reduce the clearance of  
1244 drugs eliminated predominantly by CYP2D6.

1245 Special Populations: Patients With Renal Impairment: Twelve volunteers with  
1246 chronic renal failure (mean creatinine clearance: 13 mL/min; range: 6 to 23) and another 6  
1247 individuals undergoing hemodialysis were each given a single 100-mg dose of lamotrigine. The  
1248 mean plasma half-lives determined in the study were 42.9 hours (chronic renal failure), 13.0  
1249 hours (during hemodialysis), and 57.4 hours (between hemodialysis) compared with 26.2 hours  
1250 in healthy volunteers. On average, approximately 20% (range: 5.6 to 35.1) of the amount of  
1251 lamotrigine present in the body was eliminated by hemodialysis during a 4-hour session [*see*  
1252 *Dosage and Administration (2.1)*].

1253 Hepatic Disease: The pharmacokinetics of lamotrigine following a single 100-mg  
1254 dose of lamotrigine were evaluated in 24 subjects with mild, moderate, and severe hepatic  
1255 impairment (Child-Pugh Classification system) and compared with 12 subjects without hepatic  
1256 impairment. The patients with severe hepatic impairment were without ascites (n = 2) or with  
1257 ascites (n = 5). The mean apparent clearances of lamotrigine in patients with mild (n = 12),  
1258 moderate (n = 5), severe without ascites (n = 2), and severe with ascites (n = 5) liver impairment  
1259 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  
1260 with  $0.37 \pm 0.1$  mL/min/kg in the healthy controls. Mean half-lives of lamotrigine in patients  
1261 with mild, moderate, severe without ascites, and severe with ascites hepatic impairment were  $46$   
1262  $\pm 20$ ,  $72 \pm 44$ ,  $67 \pm 11$ , and  $100 \pm 48$  hours, respectively, as compared with  $33 \pm 7$  hours in  
1263 healthy controls [*see Dosage and Administration (2.1)*].

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 46

1264 **Age: Pediatric Patients:** The pharmacokinetics of lamotrigine following a single 2-  
1265 mg/kg dose were evaluated in 2 studies of pediatric patients (n = 29 for patients 10 months to 5.9  
1266 years of age and n = 26 for patients 5 to 11 years of age). Forty-three patients received  
1267 concomitant therapy with other AEDs and 12 patients received lamotrigine as monotherapy.  
1268 Lamotrigine pharmacokinetic parameters for pediatric patients are summarized in Table 16.

1269 Population pharmacokinetic analyses involving patients 2 to 18 years of age  
1270 demonstrated that lamotrigine clearance was influenced predominantly by total body weight and  
1271 concurrent AED therapy. The oral clearance of lamotrigine was higher, on a body weight basis,  
1272 in pediatric patients than in adults. Weight-normalized lamotrigine clearance was higher in those  
1273 subjects weighing less than 30 kg, compared with those weighing greater than 30 kg.  
1274 Accordingly, patients weighing less than 30 kg may need an increase of as much as 50% in  
1275 maintenance doses, based on clinical response, as compared with subjects weighing more than  
1276 30 kg being administered the same AEDs [see *Dosage and Administration (2.2)*]. These analyses  
1277 also revealed that, after accounting for body weight, lamotrigine clearance was not significantly  
1278 influenced by age. Thus, the same weight-adjusted doses should be administered to children  
1279 irrespective of differences in age. Concomitant AEDs which influence lamotrigine clearance in  
1280 adults were found to have similar effects in children.

1281

1282 **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)

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 47

<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

1283 <sup>a</sup> Carbamazepine, phenobarbital, phenytoin, and primidone have been shown to increase the  
1284 apparent clearance of lamotrigine. Estrogen-containing oral contraceptives and rifampin have  
1285 also been shown to increase the apparent clearance of lamotrigine [*see Drug Interactions (7)*].  
1286 <sup>b</sup> Two subjects were included in the calculation for mean T<sub>max</sub>  
1287 <sup>c</sup> Parameter not estimated.

1288  
1289 *Elderly:* The pharmacokinetics of lamotrigine following a single 150-mg dose of  
1290 LAMICTAL were evaluated in 12 elderly volunteers between the ages of 65 and 76 years (mean  
1291 creatinine clearance = 61 mL/min, range: 33 to 108 mL/min). The mean half-life of lamotrigine  
1292 in these subjects was 31.2 hours (range: 24.5 to 43.4 hours), and the mean clearance was 0.40  
1293 mL/min/kg (range: 0.26 to 0.48 mL/min/kg).

1294 *Gender:* The clearance of lamotrigine is not affected by gender. However, during  
1295 dose escalation of LAMICTAL in one clinical trial in patients with epilepsy on a stable dose of  
1296 valproate (n = 77), mean trough lamotrigine concentrations, unadjusted for weight, were 24% to  
1297 45% higher (0.3 to 1.7 mcg/mL) in females than in males.

1298 *Race:* The apparent oral clearance of lamotrigine was 25% lower in non-Caucasians  
1299 than Caucasians.

### 1300 **13 NONCLINICAL TOXICOLOGY**

#### 1301 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

1302 No evidence of carcinogenicity was seen in 1 mouse study or 2 rat studies following oral  
1303 administration of lamotrigine for up to 2 years at maximum tolerated doses (30 mg/kg/day for  
1304 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>,  
1305 respectively). Steady-state plasma concentrations ranged from 1 to 4 mcg/mL in the mouse study  
1306 and 1 to 10 mcg/mL in the rat study. Plasma concentrations associated with the recommended  
1307 human doses of 300 to 500 mg/day are generally in the range of 2 to 5 mcg/mL, but  
1308 concentrations as high as 19 mcg/mL have been recorded.

1309 Lamotrigine was not mutagenic in the presence or absence of metabolic activation when  
1310 tested in 2 gene mutation assays (the Ames test and the in vitro mammalian mouse lymphoma  
1311 assay). In 2 cytogenetic assays (the in vitro human lymphocyte assay and the in vivo rat bone

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 48

1312 marrow assay), lamotrigine did not increase the incidence of structural or numerical  
1313 chromosomal abnormalities.

1314 No evidence of impairment of fertility was detected in rats given oral doses of  
1315 lamotrigine up to 2.4 times the highest usual human maintenance dose of 8.33 mg/kg/day or 0.4  
1316 times the human dose on a mg/m<sup>2</sup> basis. The effect of lamotrigine on human fertility is unknown.

## 1317 **14 CLINICAL STUDIES**

### 1318 **14.1 Epilepsy**

#### 1319 Monotherapy With LAMICTAL in Adults With Partial Seizures Already Receiving 1320 Treatment With Carbamazepine, Phenytoin, Phenobarbital, or Primidone as the Single

1321 AED: The effectiveness of monotherapy with LAMICTAL was established in a multicenter,  
1322 double-blind clinical trial enrolling 156 adult outpatients with partial seizures. The patients  
1323 experienced at least 4 simple partial, complex partial, and/or secondarily generalized seizures  
1324 during each of 2 consecutive 4-week periods while receiving carbamazepine or phenytoin  
1325 monotherapy during baseline. LAMICTAL (target dose of 500 mg/day) or valproate (1,000  
1326 mg/day) was added to either carbamazepine or phenytoin monotherapy over a 4-week period.  
1327 Patients were then converted to monotherapy with LAMICTAL or valproate during the next 4  
1328 weeks, then continued on monotherapy for an additional 12-week period.

1329 Study endpoints were completion of all weeks of study treatment or meeting an escape  
1330 criterion. Criteria for escape relative to baseline were: (1) doubling of average monthly seizure  
1331 count, (2) doubling of highest consecutive 2-day seizure frequency, (3) emergence of a new  
1332 seizure type (defined as a seizure that did not occur during the 8-week baseline) that is more  
1333 severe than seizure types that occur during study treatment, or (4) clinically significant  
1334 prolongation of generalized tonic-clonic (GTC) seizures. The primary efficacy variable was the  
1335 proportion of patients in each treatment group who met escape criteria.

1336 The percentages of patients who met escape criteria were 42% (32/76) in the group  
1337 receiving LAMICTAL and 69% (55/80) in the valproate group. The difference in the percentage  
1338 of patients meeting escape criteria was statistically significant ( $p = 0.0012$ ) in favor of  
1339 LAMICTAL. No differences in efficacy based on age, sex, or race were detected.

1340 Patients in the control group were intentionally treated with a relatively low dose of  
1341 valproate; as such, the sole objective of this study was to demonstrate the effectiveness and  
1342 safety of monotherapy with LAMICTAL, and cannot be interpreted to imply the superiority of  
1343 LAMICTAL to an adequate dose of valproate.

1344 Adjunctive Therapy With LAMICTAL in Adults With Partial Seizures: The  
1345 effectiveness of LAMICTAL as adjunctive therapy (added to other AEDs) was established in 3  
1346 multicenter, placebo-controlled, double-blind clinical trials in 355 adults with refractory partial  
1347 seizures. The patients had a history of at least 4 partial seizures per month in spite of receiving  
1348 one or more AEDs at therapeutic concentrations and, in 2 of the studies, were observed on their  
1349 established AED regimen during baselines that varied between 8 to 12 weeks. In the third,  
1350 patients were not observed in a prospective baseline. In patients continuing to have at least 4

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 49

1351 seizures per month during the baseline, LAMICTAL or placebo was then added to the existing  
1352 therapy. In all 3 studies, change from baseline in seizure frequency was the primary measure of  
1353 effectiveness. The results given below are for all partial seizures in the intent-to-treat population  
1354 (all patients who received at least one dose of treatment) in each study, unless otherwise  
1355 indicated. The median seizure frequency at baseline was 3 per week while the mean at baseline  
1356 was 6.6 per week for all patients enrolled in efficacy studies.

1357 One study (n = 216) was a double-blind, placebo-controlled, parallel trial consisting of a  
1358 24-week treatment period. Patients could not be on more than 2 other anticonvulsants and  
1359 valproate was not allowed. Patients were randomized to receive placebo, a target dose of 300  
1360 mg/day of LAMICTAL, or a target dose of 500 mg/day of LAMICTAL. The median reductions  
1361 in the frequency of all partial seizures relative to baseline were 8% in patients receiving placebo,  
1362 20% in patients receiving 300 mg/day of LAMICTAL, and 36% in patients receiving 500  
1363 mg/day of LAMICTAL. The seizure frequency reduction was statistically significant in the 500-  
1364 mg/day group compared with the placebo group, but not in the 300-mg/day group.

1365 A second study (n = 98) was a double-blind, placebo-controlled, randomized, crossover  
1366 trial consisting of two 14-week treatment periods (the last 2 weeks of which consisted of dose  
1367 tapering) separated by a 4-week washout period. Patients could not be on more than 2 other  
1368 anticonvulsants and valproate was not allowed. The target dose of LAMICTAL was 400 mg/day.  
1369 When the first 12 weeks of the treatment periods were analyzed, the median change in seizure  
1370 frequency was a 25% reduction on LAMICTAL compared with placebo ( $p < 0.001$ ).

1371 The third study (n = 41) was a double-blind, placebo-controlled, crossover trial consisting  
1372 of two 12-week treatment periods separated by a 4-week washout period. Patients could not be  
1373 on more than 2 other anticonvulsants. Thirteen patients were on concomitant valproate; these  
1374 patients received 150 mg/day of LAMICTAL. The 28 other patients had a target dose of 300  
1375 mg/day of LAMICTAL. The median change in seizure frequency was a 26% reduction on  
1376 LAMICTAL compared with placebo ( $p < 0.01$ ).

1377 No differences in efficacy based on age, sex, or race, as measured by change in seizure  
1378 frequency, were detected.

1379 **Adjunctive Therapy With LAMICTAL in Pediatric Patients With Partial Seizures:**  
1380 The effectiveness of LAMICTAL as adjunctive therapy in pediatric patients with partial seizures  
1381 was established in a multicenter, double-blind, placebo-controlled trial in 199 patients 2 to 16  
1382 years of age (n = 98 on LAMICTAL, n = 101 on placebo). Following an 8-week baseline phase,  
1383 patients were randomized to 18 weeks of treatment with LAMICTAL or placebo added to their  
1384 current AED regimen of up to 2 drugs. Patients were dosed based on body weight and valproate  
1385 use. Target doses were designed to approximate 5 mg/kg/day for patients taking valproate  
1386 (maximum dose: 250 mg/day) and 15 mg/kg/day for the patients not taking valproate (maximum  
1387 dose: 750 mg/day). The primary efficacy endpoint was percentage change from baseline in all  
1388 partial seizures. For the intent-to-treat population, the median reduction of all partial seizures

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 50

1389 was 36% in patients treated with LAMICTAL and 7% on placebo, a difference that was  
1390 statistically significant ( $p < 0.01$ ).

1391 Adjunctive Therapy With LAMICTAL in Pediatric and Adult Patients With Lennox-  
1392 Gastaut Syndrome: The effectiveness of LAMICTAL as adjunctive therapy in patients with  
1393 Lennox-Gastaut syndrome was established in a multicenter, double-blind, placebo-controlled  
1394 trial in 169 patients 3 to 25 years of age ( $n = 79$  on LAMICTAL,  $n = 90$  on placebo). Following a  
1395 4-week single-blind, placebo phase, patients were randomized to 16 weeks of treatment with  
1396 LAMICTAL or placebo added to their current AED regimen of up to 3 drugs. Patients were  
1397 dosed on a fixed-dose regimen based on body weight and valproate use. Target doses were  
1398 designed to approximate 5 mg/kg/day for patients taking valproate (maximum dose: 200 mg/day)  
1399 and 15 mg/kg/day for patients not taking valproate (maximum dose: 400 mg/day). The primary  
1400 efficacy endpoint was percentage change from baseline in major motor seizures (atonic, tonic,  
1401 major myoclonic, and tonic-clonic seizures). For the intent-to-treat population, the median  
1402 reduction of major motor seizures was 32% in patients treated with LAMICTAL and 9% on  
1403 placebo, a difference that was statistically significant ( $p < 0.05$ ). Drop attacks were significantly  
1404 reduced by LAMICTAL (34%) compared with placebo (9%), as were tonic-clonic seizures (36%  
1405 reduction versus 10% increase for LAMICTAL and placebo, respectively).

1406 Adjunctive Therapy With LAMICTAL in Pediatric and Adult Patients With Primary  
1407 Generalized Tonic-Clonic Seizures: The effectiveness of LAMICTAL as adjunctive therapy  
1408 in patients with primary generalized tonic-clonic seizures was established in a multicenter,  
1409 double-blind, placebo-controlled trial in 117 pediatric and adult patients  $\geq 2$  years ( $n = 58$  on  
1410 LAMICTAL,  $n = 59$  on placebo). Patients with at least 3 primary generalized tonic-clonic  
1411 seizures during an 8-week baseline phase were randomized to 19 to 24 weeks of treatment with  
1412 LAMICTAL or placebo added to their current AED regimen of up to 2 drugs. Patients were  
1413 dosed on a fixed-dose regimen, with target doses ranging from 3 mg/kg/day to 12 mg/kg/day for  
1414 pediatric patients and from 200 mg/day to 400 mg/day for adult patients based on concomitant  
1415 AED.

1416 The primary efficacy endpoint was percentage change from baseline in primary  
1417 generalized tonic-clonic seizures. For the intent-to-treat population, the median percent reduction  
1418 of primary generalized tonic-clonic seizures was 66% in patients treated with LAMICTAL and  
1419 34% on placebo, a difference that was statistically significant ( $p = 0.006$ ).

## 1420 **14.2 Bipolar Disorder**

1421 The effectiveness of LAMICTAL in the maintenance treatment of Bipolar I Disorder was  
1422 established in 2 multicenter, double-blind, placebo-controlled studies in adult patients who met  
1423 DSM-IV criteria for Bipolar I Disorder. Study 1 enrolled patients with a current or recent (within  
1424 60 days) depressive episode as defined by DSM-IV and Study 2 included patients with a current  
1425 or recent (within 60 days) episode of mania or hypomania as defined by DSM-IV. Both studies  
1426 included a cohort of patients (30% of 404 patients in Study 1 and 28% of 171 patients in Study  
1427 2) with rapid cycling Bipolar Disorder (4 to 6 episodes per year).

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 51

1428 In both studies, patients were titrated to a target dose of 200 mg of LAMICTAL, as add-  
1429 on therapy or as monotherapy, with gradual withdrawal of any psychotropic medications during  
1430 an 8- to 16-week open-label period. Overall 81% of 1,305 patients participating in the open-label  
1431 period were receiving 1 or more other psychotropic medications, including benzodiazepines,  
1432 selective serotonin reuptake inhibitors (SSRIs), atypical antipsychotics (including olanzapine),  
1433 valproate, or lithium, during titration of LAMICTAL. Patients with a CGI-severity score of 3 or  
1434 less maintained for at least 4 continuous weeks, including at least the final week on monotherapy  
1435 with LAMICTAL, were randomized to a placebo-controlled, double-blind treatment period for  
1436 up to 18 months. The primary endpoint was TIME (time to intervention for a mood episode or  
1437 one that was emerging, time to discontinuation for either an adverse event that was judged to be  
1438 related to Bipolar Disorder, or for lack of efficacy). The mood episode could be depression,  
1439 mania, hypomania, or a mixed episode.

1440 In Study 1, patients received double-blind monotherapy with LAMICTAL 50 mg/day (n  
1441 = 50), LAMICTAL 200 mg/day (n = 124), LAMICTAL 400 mg/day (n = 47), or placebo (n =  
1442 121). LAMICTAL (200- and 400-mg/day treatment groups combined) was superior to placebo in  
1443 delaying the time to occurrence of a mood episode. Separate analyses of the 200- and 400-  
1444 mg/day dose groups revealed no added benefit from the higher dose.

1445 In Study 2, patients received double-blind monotherapy with LAMICTAL (100 to 400  
1446 mg/day, n = 59), or placebo (n = 70). LAMICTAL was superior to placebo in delaying time to  
1447 occurrence of a mood episode. The mean dose of LAMICTAL was about 211 mg/day.

1448 Although these studies were not designed to separately evaluate time to the occurrence of  
1449 depression or mania, a combined analysis for the 2 studies revealed a statistically significant  
1450 benefit for LAMICTAL over placebo in delaying the time to occurrence of both depression and  
1451 mania, although the finding was more robust for depression.

## 1452 **16 HOW SUPPLIED/STORAGE AND HANDLING**

### 1453 **LAMICTAL (lamotrigine) Tablets**

1454 25 mg, white, scored, shield-shaped tablets debossed with “LAMICTAL” and “25”,  
1455 bottles of 100 (NDC 0173-0633-02).

1456 Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled  
1457 Room Temperature] in a dry place.

1458 100 mg, peach, scored, shield-shaped tablets debossed with “LAMICTAL” and “100”,  
1459 bottles of 100 (NDC 0173-0642-55).

1460 150 mg, cream, scored, shield-shaped tablets debossed with “LAMICTAL” and “150”,  
1461 bottles of 60 (NDC 0173-0643-60).

1462 200 mg, blue, scored, shield-shaped tablets debossed with “LAMICTAL” and “200”,  
1463 bottles of 60 (NDC 0173-0644-60).

1464 Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled  
1465 Room Temperature] in a dry place and protect from light.

1466

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 52

1467           **LAMICTAL (lamotrigine) Starter Kit for Patients Taking Valproate (Blue Kit)**  
1468           25 mg, white, scored, shield-shaped tablets debossed with “LAMICTAL” and “25”,  
1469 blisterpack of 35 tablets (NDC 0173-0633-10).

1470           Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled  
1471 Room Temperature] in a dry place.

1472           **LAMICTAL (lamotrigine) Starter Kit for Patients Taking Carbamazepine,**  
1473 **Phenytoin, Phenobarbital, or Primidone and Not Taking Valproate (Green Kit)**

1474           25 mg, white, scored, shield-shaped tablets debossed with “LAMICTAL” and “25” and  
1475 100 mg, peach, scored, shield-shaped tablets debossed with “LAMICTAL” and “100”,  
1476 blisterpack of 98 tablets (84/25-mg tablets and 14/100-mg tablets) (NDC 0173-0817-28).

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           **LAMICTAL (lamotrigine) Starter Kit for Patients Not Taking Carbamazepine,**  
1480 **Phenytoin, Phenobarbital, Primidone, or Valproate (Orange Kit)**

1481           25 mg, white, scored, shield-shaped tablets debossed with “LAMICTAL” and “25” and  
1482 100 mg, peach, scored, shield-shaped tablets debossed with “LAMICTAL” and “100”,  
1483 blisterpack of 49 tablets (42/25-mg tablets and 7/100-mg tablets) (NDC 0173-0594-02).

1484           Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled  
1485 Room Temperature] in a dry place and protect from light.

1486

1487           **LAMICTAL (lamotrigine) Chewable Dispersible Tablets**

1488           2 mg, white to off-white, round tablets debossed with “LTG” over “2”, bottles of 30  
1489 (NDC 0173-0699-00). ORDER DIRECTLY FROM GlaxoSmithKline 1-800-334-4153.

1490           5 mg, white to off-white, caplet-shaped tablets debossed with “GX CL2”, bottles of 100  
1491 (NDC 0173-0526-00).

1492           25 mg, white, super elliptical-shaped tablets debossed with “GX CL5”, bottles of 100  
1493 (NDC 0173-0527-00).

1494           Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled  
1495 Room Temperature] in a dry place.

1496

1497           **LAMICTAL ODT (lamotrigine) Orally Disintegrating Tablets**

1498           25 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with “LMT”  
1499 on one side and “25” on the other, Maintenance Packs of 30 (NDC 0173-0772-02).

1500           50 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with “LMT”  
1501 on one side and “50” on the other, Maintenance Packs of 30 (NDC 0173-0774-02).

1502           100 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with  
1503 “LAMICTAL” on one side and “100” on the other, Maintenance Packs of 30 (NDC 0173-0776-  
1504 02).

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 53

1505 200 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with  
1506 “LAMICTAL” on one side and “200” on the other, Maintenance Packs of 30 (NDC 0173-0777-  
1507 02).

1508 Store between 20°C to 25°C (68°F to 77°F); with excursions permitted between 15°C and  
1509 30°C (59°F and 86°F).

1510 **LAMICTAL ODT (lamotrigine) Patient Titration Kit for Patients Taking Valproate**  
1511 **(Blue ODT Kit)**

1512 25 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with “LMT”  
1513 on one side and “25” on the other, and 50 mg, white to off-white, round, flat-faced, radius edge,  
1514 tablets debossed with “LMT” on one side and “50” on the other, blisterpack of 28 tablets  
1515 (21/25-mg tablets and 7/50-mg tablets) (NDC 0173-0779-00).

1516 **LAMICTAL ODT (lamotrigine) Patient Titration Kit for Patients Taking**  
1517 **Carbamazepine, Phenytoin, Phenobarbital, or Primidone and Not Taking Valproate**  
1518 **(Green ODT Kit)**

1519 50 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with “LMT”  
1520 on one side and “50” on the other, and 100 mg, white to off-white, round, flat-faced, radius edge,  
1521 tablets debossed with “LAMICTAL” on one side and “100” on the other, blisterpack of 56  
1522 tablets (42/50-mg tablets and 14/100-mg tablets) (NDC 0173-0780-00).

1523 **LAMICTAL ODT (lamotrigine) Patient Titration Kit for Patients Not Taking**  
1524 **Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate (Orange 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, 50 mg, white to off-white, round, flat-faced, radius edge,  
1527 tablets debossed with “LMT” on one side and “50” on the other, and 100 mg, white to off-white,  
1528 round, flat-faced, radius edge, tablets debossed with “LAMICTAL” on one side and “100” on the  
1529 other, blisterpack of 35 (14/25-mg tablets, 14/50-mg tablets, and 7/100-mg tablets) (NDC 0173-  
1530 0778-00).

1531 Store between 20°C to 25°C (68°F to 77°F); with excursions permitted between 15°C and  
1532 30°C (59°F and 86°F).

1533 **Blisterpacks:** If the product is dispensed in a blisterpack, the patient should be advised to  
1534 examine the blisterpack before use and not use if blisters are torn, broken, or missing.

## 1535 **17 PATIENT COUNSELING INFORMATION**

1536 See Medication Guide that accompanies the product.

### 1537 **17.1 Rash**

1538 Prior to initiation of treatment with LAMICTAL, the patient should be instructed that a  
1539 rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy) may herald a  
1540 serious medical event and that the patient should report any such occurrence to a physician  
1541 immediately.

### 1542 **17.2 Multiorgan Hypersensitivity Reactions, Blood Dyscrasias and Organ Failure**

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 54

1543 Patients should be instructed that multiorgan hypersensitivity reactions and acute  
1544 multiorgan failure may occur with LAMICTAL. Isolated organ failure or isolated blood  
1545 dyscrasias without evidence of multiorgan hypersensitivity may also occur. Patients should  
1546 contact their physician immediately if they experience any signs or symptoms of these conditions  
1547 [*see Warnings and Precautions (5.2, 5.3)*].

### 1548 **17.3 Suicidal Thinking and Behavior**

1549 Patients, their caregivers, and families should be counseled that AEDs, including  
1550 LAMICTAL, may increase the risk of suicidal thoughts and behavior and should be advised of  
1551 the need to be alert for the emergence or worsening of symptoms of depression, any unusual  
1552 changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about  
1553 self-harm. Behaviors of concern should be reported immediately to healthcare providers.

### 1554 **17.4 Worsening of Seizures**

1555 Patients should be advised to notify their physician if worsening of seizure control  
1556 occurs.

### 1557 **17.5 CNS Adverse Effects**

1558 Patients should be advised that LAMICTAL may cause dizziness, somnolence, and other  
1559 symptoms and signs of central nervous system (CNS) depression. Accordingly, they should be  
1560 advised neither to drive a car nor to operate other complex machinery until they have gained  
1561 sufficient experience on LAMICTAL to gauge whether or not it adversely affects their mental  
1562 and/or motor performance.

### 1563 **17.6 Pregnancy**

1564 Patients should be advised to notify their physicians if they become pregnant or intend to  
1565 become pregnant during therapy. Patients should be advised to notify their physicians if they  
1566 intend to breastfeed or are breastfeeding an infant.

1567 Patients should also be encouraged to enroll in the NAAED Pregnancy Registry if they  
1568 become pregnant. This registry is collecting information about the safety of antiepileptic drugs  
1569 during pregnancy. To enroll, patients can call the toll-free number 1-888-233-2334 [*see Use in*  
1570 *Specific Populations (8.1)*].

### 1571 **17.7 Oral Contraceptive Use**

1572 Women should be advised to notify their physician if they plan to start or stop use of oral  
1573 contraceptives or other female hormonal preparations. Starting estrogen-containing oral  
1574 contraceptives may significantly decrease lamotrigine plasma levels and stopping estrogen-  
1575 containing oral contraceptives (including the “pill-free” week) may significantly increase  
1576 lamotrigine plasma levels [*see Warnings and Precautions (5.8), Clinical Pharmacology (12.3)*].  
1577 Women should also be advised to promptly notify their physician if they experience adverse  
1578 reactions or changes in menstrual pattern (e.g., break-through bleeding) while receiving  
1579 LAMICTAL in combination with these medications.

### 1580 **17.8 Discontinuing LAMICTAL**

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 55

1581 Patients should be advised to notify their physician if they stop taking LAMICTAL for  
1582 any reason and not to resume LAMICTAL without consulting their physician.

### 1583 **17.9 Aseptic Meningitis**

1584 Patients should be advised that LAMICTAL may cause aseptic meningitis. Patients  
1585 should be advised to notify their physician immediately if they develop signs and symptoms of  
1586 meningitis such as headache, fever, nausea, vomiting, stiff neck, rash, abnormal sensitivity to  
1587 light, myalgia, chills, confusion, or drowsiness while taking LAMICTAL.

### 1588 **17.10 Potential Medication Errors**

1589 Medication errors involving LAMICTAL have occurred. In particular the names  
1590 LAMICTAL or lamotrigine can be confused with the names of other commonly used  
1591 medications. Medication errors may also occur between the different formulations of  
1592 LAMICTAL. To reduce the potential of medication errors, write and say LAMICTAL clearly.  
1593 Depictions of the LAMICTAL Tablets, Chewable Dispersible Tablets, and Orally Disintegrating  
1594 Tablets can be found in the Medication Guide that accompanies the product to highlight the  
1595 distinctive markings, colors, and shapes that serve to identify the different presentations of the  
1596 drug and thus may help reduce the risk of medication errors. **To avoid a medication error of**  
1597 **using the wrong drug or formulation, patients should be strongly advised to visually**  
1598 **inspect their tablets to verify that they are LAMICTAL, as well as the correct formulation**  
1599 **of LAMICTAL, each time they fill their prescription** [*see Dosage Forms and Strengths (3.1,*  
1600 *3.2, 3.3), How Supplied/Storage and Handling (16)*].

1601  
1602



1603  
1604 GlaxoSmithKline  
1605 Research Triangle Park, NC 27709

1606  
1607 LAMICTAL Tablets and Chewable Dispersible Tablets are manufactured by  
1608 DSM Pharmaceuticals, Inc., Greenville, NC 27834 or  
1609 GlaxoSmithKline, Research Triangle Park, NC 27709

1610  
1611 LAMICTAL Orally Disintegrating Tablets are manufactured by  
1612 Eurand, Inc., Vandalia, OH 45377

1613  
1614 LAMICTAL is a registered trademark of GlaxoSmithKline.

1615  
1616 Microcaps and AdvaTab are registered trademarks of Eurand, Inc.

1617  
1618 ©2011, GlaxoSmithKline. All rights reserved.

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 56

1619

1620 Month Year

1621 LMT:xPI

1622

1623

## MEDICATION GUIDE

1624

1625 **LAMICTAL<sup>®</sup> (la-MIK-tal) (lamotrigine) Tablets and Chewable Dispersible Tablets**

1626 **LAMICTAL<sup>®</sup> ODT<sup>™</sup> (lamotrigine) Orally Disintegrating Tablets**

1627

1628 Read this Medication Guide before you start taking LAMICTAL and each time you get a refill.

1629 There may be new information. This information does not take the place of talking with your

1630 healthcare provider about your medical condition or treatment. If you have questions about

1631 LAMICTAL, ask your healthcare provider or pharmacist.

1632

1633 **What is the most important information I should know about LAMICTAL?**

1634 **1. LAMICTAL may cause a serious skin rash that may cause you to be hospitalized or to**  
1635 **stop LAMICTAL; it may rarely cause death.**

1636 There is no way to tell if a mild rash will develop into a more serious reaction. These serious  
1637 skin reactions are more likely to happen when you begin taking LAMICTAL, within the first  
1638 2 to 8 weeks of treatment. But it can happen in people who have taken LAMICTAL for any  
1639 period of time. Children between 2 to 16 years of age have a higher chance of getting this  
1640 serious skin reaction while taking LAMICTAL.

1641 The risk of getting a rash is higher if you:

- 1642 • take LAMICTAL while taking valproate (DEPAKENE (valproic acid) or DEPAKOTE
- 1643 (divalproex sodium))
- 1644 • take a higher starting dose of LAMICTAL than your healthcare provider prescribed
- 1645 • increase your dose of LAMICTAL faster than prescribed.

1646 **LAMICTAL can also cause other types of allergic reactions or serious problems which**  
1647 **may affect organs and other parts of your body like the liver or blood cells. You may or**  
1648 **may not have a rash with these types of reactions.**

1649 **Call your healthcare provider right away if you have any of the following:**

- 1650 • **a skin rash**
- 1651 • **hives**
- 1652 • **fever**
- 1653 • **swollen lymph glands**
- 1654 • **painful sores in the mouth or around your eyes**
- 1655 • **swelling of your lips or tongue**
- 1656 • **yellowing of your skin or eyes**

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 57

- 1657 • **unusual bruising or bleeding**
- 1658 • **severe fatigue or weakness**
- 1659 • **severe muscle pain**
- 1660 • **frequent infections**

1661 These symptoms may be the first signs of a serious reaction. A healthcare provider should  
1662 examine you to decide if you should continue taking LAMICTAL.

1663 **2. Like other antiepileptic drugs, LAMICTAL may cause suicidal thoughts or actions in a**  
1664 **very small number of people, about 1 in 500.**

1665 **Call a healthcare provider right away if you have any of these symptoms, especially if**  
1666 **they are new, worse, or worry you:**

- 1667 • thoughts about suicide or dying
- 1668 • attempt to commit suicide
- 1669 • new or worse depression
- 1670 • new or worse anxiety
- 1671 • feeling agitated or restless
- 1672 • panic attacks
- 1673 • trouble sleeping (insomnia)
- 1674 • new or worse irritability
- 1675 • acting aggressive, being angry, or violent
- 1676 • acting on dangerous impulses
- 1677 • an extreme increase in activity and talking (mania)
- 1678 • other unusual changes in behavior or mood

1679 **Do not stop LAMICTAL without first talking to a healthcare provider.**

- 1680 • Stopping LAMICTAL suddenly can cause serious problems.
- 1681 • Suicidal thoughts or actions can be caused by things other than medicines. If you have  
1682 suicidal thoughts or actions, your healthcare provider may check for other causes.

1683 **How can I watch for early symptoms of suicidal thoughts and actions?**

- 1684 • Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or  
1685 feelings.
- 1686 • Keep all follow-up visits with your healthcare provider as scheduled.
- 1687 • Call your healthcare provider between visits as needed, especially if you are worried  
1688 about symptoms.

1689 **3. LAMICTAL may rarely cause aseptic meningitis, a serious inflammation of the**  
1690 **protective membrane that covers the brain and spinal cord.**

1691 **Call your healthcare provider right away if you have any of the following symptoms:**

- 1692 • Headache
- 1693 • Fever

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 58

- 1694 • Nausea
- 1695 • Vomiting
- 1696 • Stiff neck
- 1697 • Rash
- 1698 • Unusual sensitivity to light
- 1699 • Muscle pains
- 1700 • Chills
- 1701 • Confusion
- 1702 • Drowsiness

1703 Meningitis has many causes other than LAMICTAL, which your doctor would check for if  
1704 you developed meningitis while taking LAMICTAL.

1705 **LAMICTAL can have other serious side effects.** For more information ask your healthcare  
1706 provider or pharmacist. Tell your healthcare provider if you have any side effect that bothers  
1707 you. Be sure to read the section below entitled “What are the possible side effects of  
1708 LAMICTAL?”





1709 **4. Patients prescribed LAMICTAL have sometimes been given the wrong medicine**  
1710 **because many medicines have names similar to LAMICTAL, so always check that you**  
1711 **receive LAMICTAL.**

1712 Taking the wrong medication can cause serious health problems. When your healthcare  
1713 provider gives you a prescription for LAMICTAL:

- 1714 • Make sure you can read it clearly.
- 1715 • Talk to your pharmacist to check that you are given the correct medicine.
- 1716 • Each time you fill your prescription, check the tablets you receive against the pictures of  
1717 the tablets below.

1718 These pictures show the distinct wording, colors, and shapes of the tablets that help to  
1719 identify the right strength of LAMICTAL Tablets, Chewable Dispersible Tablets, and  
1720 Orally Disintegrating Tablets. Immediately call your pharmacist if you receive a  
1721 LAMICTAL tablet that does not look like one of the tablets shown below, as you may  
1722 have received the wrong medication.




1723 **LAMICTAL (lamotrigine) Tablets**

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

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 59





1724

**LAMICTAL (lamotrigine) Chewable Dispersible Tablets**

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

1725

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

 <b>25 mg, white to</b> <b>off-white</b> <b>Imprinted with</b> <b>LMT on one side</b> <b>25 on the other</b>	 <b>50 mg, white to</b> <b>off-white</b> <b>Imprinted with</b> <b>LMT on one side</b> <b>50 on the other</b>	 <b>100 mg, white to</b> <b>off-white</b> <b>Imprinted with</b> <b>LAMICTAL on</b> <b>one side</b> <b>100 on the other</b>	 <b>200 mg, white to</b> <b>off-white</b> <b>Imprinted with</b> <b>LAMICTAL on</b> <b>one side</b> <b>200 on the other</b>
--	--	--	---

1726

1727

**What is LAMICTAL?**

1728

LAMICTAL is a prescription medicine used:

1729

1. together with other medicines to treat certain types of seizures (partial seizures, primary generalized tonic-clonic seizures, generalized seizures of Lennox-Gastaut syndrome) in people 2 years or older.

1730

1731

1732

2. alone when changing from other medicines used to treat partial seizures in people 16 years or older.

1733

1734

3. for the long-term treatment of Bipolar I Disorder to lengthen the time between mood episodes in people 18 years or older who have been treated for mood episodes with other medicine.

1735

1736

1737

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

1738

1739

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

1740

1741

1742

**Who should not take LAMICTAL?**

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 60

1743 You should not take LAMICTAL if you have had an allergic reaction to lamotrigine or to any of  
1744 the inactive ingredients in LAMICTAL. See the end of this leaflet for a complete list of  
1745 ingredients in LAMICTAL.

1746

### 1747 **What should I tell my healthcare provider before taking LAMICTAL?**

1748 Before taking LAMICTAL, tell your healthcare provider about all of your medical conditions,  
1749 including if you:

- 1750 • have had a rash or allergic reaction to another antiseizure medicine.
- 1751 • have or have had depression, mood problems or suicidal thoughts or behavior.
- 1752 • are taking oral contraceptives (birth control pills) or other female hormonal medicines. Do  
1753 not start or stop taking birth control pills or other female hormonal medicine until you have  
1754 talked with your healthcare provider. Tell your healthcare provider if you have any changes  
1755 in your menstrual pattern such as breakthrough bleeding. Stopping or starting these  
1756 medicines may cause side effects (such as dizziness, lack of coordination, or double vision)  
1757 or lessen how well LAMICTAL works.
- 1758 • are pregnant or plan to become pregnant. It is not known if LAMICTAL will harm your  
1759 unborn baby. If you become pregnant while taking LAMICTAL, talk to your healthcare  
1760 provider about registering with the North American Antiepileptic Drug Pregnancy Registry.  
1761 You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to  
1762 collect information about the safety of antiepileptic drugs during pregnancy.
- 1763 • are breastfeeding. LAMICTAL can pass into your breast milk. You and your healthcare  
1764 provider should decide if you should take LAMICTAL or breastfeed. Breastfeeding while  
1765 taking LAMICTAL is not recommended.

1766 Tell your healthcare provider about all the medicines you take or if you are planning to take a  
1767 new medicine, including prescription and non-prescription medicines, vitamins, and herbal  
1768 supplements. Using LAMICTAL with certain other medicines can affect each other, causing side  
1769 effects.

1770

### 1771 **How should I take LAMICTAL?**

- 1772 • Take LAMICTAL exactly as prescribed.
- 1773 • Your healthcare provider may change your dose. Do not change your dose without talking to  
1774 your healthcare provider.
- 1775 • Do not stop taking LAMICTAL without talking to your healthcare provider. Stopping  
1776 LAMICTAL suddenly may cause serious problems. For example, if you have epilepsy and  
1777 you stop taking LAMICTAL suddenly, you may get seizures that do not stop. Talk with your  
1778 healthcare provider about how to stop LAMICTAL slowly.
- 1779 • If you miss a dose of LAMICTAL, take it as soon as you remember. If it is almost time for  
1780 your next dose, just skip the missed dose. Take the next dose at your regular time. **Do not**

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 61

1781        **take two doses at the same time.**

- 1782        • You may not feel the full effect of LAMICTAL for several weeks.
- 1783        • If you have epilepsy, tell your healthcare provider if your seizures get worse or if you have
- 1784        any new types of seizures.
- 1785        • Swallow LAMICTAL tablets whole.
- 1786        • If you have trouble swallowing LAMICTAL Tablets, there may be another form of
- 1787        LAMICTAL you can take.
- 1788        • LAMICTAL ODT should be placed on the tongue and moved around the mouth. The tablet
- 1789        will rapidly disintegrate, can be swallowed with or without water, and can be taken with or
- 1790        without food.
- 1791        • LAMICTAL Chewable Dispersible tablets may be swallowed whole, chewed, or mixed in
- 1792        water or diluted fruit juice. If the tablets are chewed, drink a small amount of water or diluted
- 1793        fruit juice to help in swallowing. To break up LAMICTAL Chewable Dispersible tablets, add
- 1794        the tablets to a small amount of liquid (1 teaspoon, or enough to cover the medicine) in a
- 1795        glass or spoon. Wait at least 1 minute or until the tablets are completely broken up, mix the
- 1796        solution together and take the whole amount right away.
- 1797        • If you receive LAMICTAL in a blisterpack, examine the blisterpack before use. Do not use if
- 1798        blisters are torn, broken, or missing.
- 1799

1800        **What should I avoid while taking LAMICTAL?**

- 1801        • Do not drive a car or operate complex, hazardous machinery until you know how
- 1802        LAMICTAL affects you.
- 1803

1804        **What are possible side effects of LAMICTAL?**

- 1805        • See “What is the most important information I should know about LAMICTAL?”

1806        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

1807        Tell your healthcare provider about any side effect that bothers you or that does not go away.

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 62

1808 These are not all the possible side effects of LAMICTAL. For more information, ask your  
1809 healthcare provider or pharmacist.

1810 Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-  
1811 800-FDA-1088.

1812

### 1813 **How should I store LAMICTAL?**

1814 • Store LAMICTAL at room temperature between 68°F to 77°F (20°C to 25°C).

1815 • **Keep LAMICTAL and all medicines out of the reach of children.**

1816

### 1817 **General information about LAMICTAL**

1818 Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

1819 Do not use LAMICTAL for a condition for which it was not prescribed. Do not give

1820 LAMICTAL to other people, even if they have the same symptoms you have. It may harm them.

1821 This Medication Guide summarizes the most important information about LAMICTAL. If you

1822 would like more information, talk with your healthcare provider. You can ask your healthcare

1823 provider or pharmacist for information about LAMICTAL that is written for healthcare

1824 professionals.

1825 For more information, go to [www.lamictal.com](http://www.lamictal.com) or call 1-888-825-5249.

1826

### 1827 **What are the ingredients in LAMICTAL?**

#### 1828 **LAMICTAL Tablets**

1829 Active ingredient: lamotrigine.

1830 Inactive ingredients: lactose; magnesium stearate, microcrystalline cellulose, povidone, sodium

1831 starch glycolate, FD&C Yellow No. 6 Lake (100-mg tablet only), ferric oxide, yellow (150-mg

1832 tablet only), and FD&C Blue No. 2 Lake (200-mg tablet only).

#### 1833 **LAMICTAL Chewable Dispersible Tablets**

1834 Active ingredient: lamotrigine.

1835 Inactive ingredients: blackcurrant flavor, calcium carbonate, low-substituted

1836 hydroxypropylcellulose, magnesium aluminum silicate, magnesium stearate, povidone, saccharin

1837 sodium, and sodium starch glycolate.

#### 1838 **LAMICTAL ODT Orally Disintegrating Tablets**

1839 Active ingredient: lamotrigine.

1840 Inactive ingredients: artificial cherry flavor, crospovidone, ethylcellulose, magnesium stearate,

1841 mannitol, polyethylene, and sucralose.

1842

NDA 020241/S-047  
NDA 020764/S-040  
NDA 022251/S-010  
FDA Approved Labeling Text dated 7/28/2011  
Page 63

1843 **This Medication Guide has been approved by the U.S. Food and Drug Administration.**

1844

1845



1846

1847 GlaxoSmithKline

1848 Research Triangle Park, NC 27709

1849

1850 LAMICTAL Tablets and Chewable Dispersible Tablets are manufactured by

1851 DSM Pharmaceuticals, Inc.,

1852 Greenville, NC 27834 or

1853 GlaxoSmithKline

1854 Research Triangle Park, NC 27709

1855

1856 LAMICTAL Orally Disintegrating Tablets are manufactured by

1857 Eurand, Inc., Vandalia, OH 45377

1858

1859 LAMICTAL is a registered trademark of GlaxoSmithKline.

1860 DEPAKENE and DEPAKOTE are registered trademarks of Abbott Laboratories.

1861

1862 ©2010, GlaxoSmithKline. All rights reserved.

1863

1864 October 2010

1865 LMT:3MG