

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
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 and toxic epidermal necrolysis, and/or rash-related death have been caused by lamotrigine. The rate of serious rash is greater in pediatric patients than in adults. Additional factors that may increase the risk of rash include:
 - coadministration with valproate.
 - exceeding recommended initial dose of LAMICTAL.
 - exceeding recommended dose escalation for LAMICTAL. (5.1)
- Benign rashes are also caused by lamotrigine; 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

Dosage and Administration (2.1, 2.2, 2.4) 12/2014

INDICATIONS AND USAGE

LAMICTAL is an antiepileptic drug (AED) indicated for:

Epilepsy—adjunctive therapy in patients aged 2 years and older:

- partial-onset seizures.
- primary generalized tonic-clonic seizures.
- generalized seizures of Lennox-Gastaut syndrome. (1.1)

Epilepsy—monotherapy in patients aged 16 years and older: Conversion to monotherapy in patients with partial-onset seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single AED. (1.1)

Bipolar disorder in patients aged 18 years and older: 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. (2.1, 2.2, 2.3, 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, 5.1)
- Adjustments to maintenance doses will be necessary in most patients starting or stopping estrogen-containing oral contraceptives. (2.1, 5.8)
- Discontinuation: Taper over a period of at least 2 weeks (approximately 50% dose reduction per week). (2.1, 5.9)

Epilepsy:

- Adjunctive therapy—See Table 1 for patients older than 12 years and Tables 2 and 3 for patients aged 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: Discontinue at the first sign of rash, unless the rash is clearly not drug related. (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. Monitor for signs of anemia, unexpected infection, or bleeding. (5.3)
- Suicidal behavior and ideation: Monitor for suicidal thoughts or behaviors. (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: Monitor for signs of meningitis. (5.6)
- Medication errors due to product name confusion: Strongly advise patients to visually inspect tablets to verify the received drug is correct. (3.4, 5.7, 16, 17)

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

- Valproate increases lamotrigine concentrations more than 2-fold. (7, 12.3)
- Carbamazepine, phenytoin, phenobarbital, primidone, and rifampin decrease lamotrigine concentrations by approximately 40%. (7, 12.3)
- Estrogen-containing oral contraceptives decrease lamotrigine concentrations by approximately 50%. (7, 12.3)
- Protease inhibitors lopinavir/ritonavir and atazanavir/lopinavir decrease lamotrigine exposure by approximately 50% and 32%, respectively. (7, 12.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data may cause fetal harm. (8.1)
- Efficacy of LAMICTAL, used as adjunctive treatment for partial-onset seizures, was not demonstrated in a small, randomized, double-blind, placebo-controlled trial in very young pediatric patients (1 to 24 months). (8.4)
- Hepatic impairment: Dosage adjustments required in patients with moderate and severe liver impairment. (2.1, 8.6)
- Renal impairment: Reduced maintenance doses may be effective for patients with significant renal impairment. (2.1, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2014

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 2

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: SERIOUS SKIN RASHES

1 INDICATIONS AND USAGE

- 1.1 Epilepsy
- 1.2 Bipolar Disorder

2 DOSAGE AND ADMINISTRATION

- 2.1 General Dosing Considerations
- 2.2 Epilepsy—Adjunctive Therapy
- 2.3 Epilepsy—Conversion From Adjunctive Therapy to Monotherapy
- 2.4 Bipolar Disorder
- 2.5 Administration of LAMICTAL Chewable Dispersible Tablets
- 2.6 Administration of LAMICTAL ODT Orally Disintegrating Tablets

3 DOSAGE FORMS AND STRENGTHS

- 3.1 Tablets
- 3.2 Chewable Dispersible Tablets
- 3.3 Orally Disintegrating Tablets
- 3.4 Potential Medication Errors

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Serious Skin Rashes [see *Boxed Warning*]
- 5.2 Multiorgan Hypersensitivity Reactions and Organ Failure
- 5.3 Blood Dyscrasias
- 5.4 Suicidal Behavior and Ideation
- 5.5 Use in Patients With Bipolar Disorder
- 5.6 Aseptic Meningitis
- 5.7 Potential Medication Errors
- 5.8 Concomitant Use With Oral Contraceptives
- 5.9 Withdrawal Seizures
- 5.10 Status Epilepticus
- 5.11 Sudden Unexplained Death in Epilepsy (SUDEP)

5.12 Addition of LAMICTAL to a Multidrug Regimen That Includes Valproate

5.13 Binding in the Eye and Other Melanin-Containing Tissues

5.14 Laboratory Tests

6 ADVERSE REACTIONS

- 6.1 Clinical Trial Experience
- 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

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

1 FULL PRESCRIBING INFORMATION

2 WARNING: SERIOUS SKIN RASHES
3 LAMICTAL[®] 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 (aged 2 to 16
6 years) 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 (aged 2 to 16 years) 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.

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 3

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 aged 2 years and older:

- 34 • partial-onset seizures.
- 35 • primary generalized tonic-clonic (PGTC) seizures.
- 36 • generalized seizures of Lennox-Gastaut syndrome.

37 Monotherapy: LAMICTAL is indicated for conversion to monotherapy in adults (aged
38 16 years and older) with partial-onset seizures who are receiving treatment with carbamazepine,
39 phenytoin, 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 (aged 18 years and older) treated for acute mood episodes with standard therapy. The
48 effectiveness of 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.

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 4

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 for LAMICTAL is exceeded and in patients with a history of allergy
64 or rash to other AEDs.

65 LAMICTAL Starter Kits and LAMICTAL ODT[®] 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 (older than 12 years)
68 and bipolar I disorder (aged 18 years and older) and are intended to help reduce the potential for
69 rash. The use of LAMICTAL Starter Kits and LAMICTAL ODT Patient Titration Kits is
70 recommended for appropriate patients who are starting or restarting LAMICTAL [see *How*
71 *Supplied/Storage 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 LAMICTAL,
75 the need to restart with the initial dosing recommendations should be assessed. The greater the
76 interval of time since the previous dose, the greater consideration should be given to restarting
77 with the initial dosing recommendations. If a patient has discontinued lamotrigine for a period of
78 more than 5 half-lives, it is recommended that initial dosing recommendations and guidelines be
79 followed. The half-life of lamotrigine is affected by other concomitant medications [see *Clinical*
80 *Pharmacology (12.3)*].

81 LAMICTAL Added to Drugs Known to Induce or Inhibit Glucuronidation: Because
82 lamotrigine is metabolized predominantly by glucuronic acid conjugation, drugs that are known
83 to induce or inhibit glucuronidation may affect the apparent clearance of lamotrigine. Drugs that
84 induce glucuronidation include carbamazepine, phenytoin, phenobarbital, primidone, rifampin,
85 estrogen-containing oral contraceptives, and the protease inhibitors lopinavir/ritonavir and
86 atazanavir/ritonavir. Valproate inhibits glucuronidation. For dosing considerations for
87 LAMICTAL in patients on estrogen-containing contraceptives and atazanavir/ritonavir, see
88 below and Table 13. For dosing considerations for LAMICTAL in patients on other drugs known
89 to induce or inhibit glucuronidation, see Table 1, Table 2, Table 5, Table 6, and Table 13.

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

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 5

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

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

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

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

130 (3) *Stopping Estrogen-Containing Oral Contraceptives:* In women not taking
131 carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin and the

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 6

132 protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir that induce lamotrigine
133 glucuronidation [*see Drug Interactions (7), Clinical Pharmacology (12.3)*], the maintenance
134 dose of LAMICTAL will in most cases need to be decreased by as much as 50% in order to
135 maintain a consistent lamotrigine plasma level. The decrease in dose of LAMICTAL should not
136 exceed 25% of the total daily dose per week over a 2-week period, unless clinical response or
137 lamotrigine plasma levels indicate otherwise [*see Clinical Pharmacology (12.3)*]. In women
138 taking LAMICTAL in addition to carbamazepine, phenytoin, phenobarbital, primidone, or other
139 | drugs such as rifampin and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir
140 that induce lamotrigine glucuronidation [*see Drug Interactions (7), Clinical Pharmacology*
141 (*12.3*)], no adjustment to the dose of LAMICTAL should be necessary.

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

149 Patients Taking Atazanavir/Ritonavir: While atazanavir/ritonavir does reduce the
150 lamotrigine plasma concentration, no adjustments to the recommended dose-escalation
151 guidelines for LAMICTAL should be necessary solely based on the use of atazanavir/ritonavir.
152 Dose escalation should follow the recommended guidelines for initiating adjunctive therapy with
153 LAMICTAL based on concomitant AED or other concomitant medications (see Tables 1, 2, and
154 5). In patients already taking maintenance doses of LAMICTAL and not taking glucuronidation
155 inducers, the dose of LAMICTAL may need to be increased if atazanavir/ritonavir is added, or
156 decreased if atazanavir/ritonavir is discontinued [*see Clinical Pharmacology (12.3)*].

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

165 Patients With Renal Impairment: Initial doses of LAMICTAL should be based on
166 patients' concomitant medications (see Tables 1-3 or Table 5); reduced maintenance doses may
167 be effective for patients with significant renal impairment [*see Use in Specific Populations (8.7),*
168 *Clinical Pharmacology (12.3)*]. Few patients with severe renal impairment have been evaluated
169 during chronic treatment with LAMICTAL. Because there is inadequate experience in this
170 population, LAMICTAL should be used with caution in these patients.

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 7

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

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

177 Discontinuing carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such
178 as rifampin and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir that induce
179 lamotrigine glucuronidation should prolong the half-life of lamotrigine; discontinuing valproate
180 should shorten the half-life of lamotrigine.

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

189 **2.2 Epilepsy—Adjunctive Therapy**

190 This section provides specific dosing recommendations for patients older than 12 years
191 and patients aged 2 to 12 years. Within each of these age-groups, specific dosing
192 recommendations are provided depending upon concomitant AEDs or other concomitant
193 medications (see Table 1 for patients older than 12 years and Table 2 for patients aged 2 to
194 12 years). A weight-based dosing guide for patients aged 2 to 12 years on concomitant valproate
195 is provided in Table 3.

196 **Patients Older Than 12 Years:** Recommended dosing guidelines are summarized in
197 Table 1.

198

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 8

199 **Table 1. Escalation Regimen for LAMICTAL in Patients Older Than 12 Years With**
200 **Epilepsy**

	In Patients TAKING Valproate^a	In Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone,^b or Valproate^a	In Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone^b and NOT TAKING Valproate^a
Weeks 1 and 2	25 mg every <i>other</i> day	25 mg every day	50 mg/day
Weeks 3 and 4	25 mg every day	50 mg/day	100 mg/day (in 2 divided doses)
Week 5 onward to maintenance	Increase by 25 to 50 mg/day every 1 to 2 weeks.	Increase by 50 mg/day every 1 to 2 weeks.	Increase by 100 mg/day every 1 to 2 weeks.
Usual maintenance dose	100 to 200 mg/day with valproate alone 100 to 400 mg/day with valproate and other drugs that induce glucuronidation (in 1 or 2 divided doses)	225 to 375 mg/day (in 2 divided doses)	300 to 500 mg/day (in 2 divided doses)

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

203 ^b Drugs that induce lamotrigine glucuronidation and increase clearance, other than the specified
204 antiepileptic drugs, include estrogen-containing oral contraceptives, rifampin, and the protease
205 inhibitors lopinavir/ritonavir and atazanavir/ritonavir. Dosing recommendations for oral
206 contraceptives and the protease inhibitor atazanavir/ritonavir can be found in General Dosing
207 Considerations [*see Dosage and Administration (2.1)*]. Patients on rifampin and the protease
208 inhibitor lopinavir/ritonavir should follow the same dosing titration/maintenance regimen used
209 with antiepileptic drugs that induce glucuronidation and increase clearance [*see Dosage and*
210 *Administration (2.1), Drug Interactions (7), and Clinical Pharmacology (12.3)*].

211
212 Patients Aged 2 to 12 Years: Recommended dosing guidelines are summarized in
213 Table 2.

214 Smaller starting doses and slower dose escalations than those used in clinical trials are
215 recommended because of the suggestion that the risk of rash may be decreased by smaller
216 starting doses and slower dose escalations. Therefore, maintenance doses will take longer to

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 9

217 reach in clinical practice than in clinical trials. It may take several weeks to months to achieve an
218 individualized maintenance dose. Maintenance doses in patients weighing less than 30 kg,
219 regardless of age or concomitant AED, may need to be increased as much as 50%, based on
220 clinical response.

221 **The smallest available strength of LAMICTAL Chewable Dispersible Tablets is**
222 **2 mg, and only whole tablets should be administered. If the calculated dose cannot be**
223 **achieved using whole tablets, the dose should be rounded down to the nearest whole tablet**
224 *[see How Supplied/Storage and Handling (16) and Medication Guide].*

225

226 **Table 2. Escalation Regimen for LAMICTAL in Patients Aged 2 to 12 Years With Epilepsy**

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

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 10

Week 5 onward to maintenance	The dose should be increased every 1 to 2 weeks as follows: calculate 0.3 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily dose.	The dose should be increased every 1 to 2 weeks as follows: calculate 0.6 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily dose.	The dose should be increased every 1 to 2 weeks as follows: calculate 1.2 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily dose.
Usual maintenance dose	1 to 5 mg/kg/day (maximum 200 mg/day in 1 or 2 divided doses) 1 to 3 mg/kg/day with valproate alone	4.5 to 7.5 mg/kg/day (maximum 300 mg/day in 2 divided doses)	5 to 15 mg/kg/day (maximum 400 mg/day in 2 divided doses)
Maintenance dose in patients less than 30 kg	May need to be increased by as much as 50%, based on clinical response.	May need to be increased by as much as 50%, based on clinical response.	May need to be increased by as much as 50%, based on clinical response.

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

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

230 ^b Drugs that induce lamotrigine glucuronidation and increase clearance, other than the specified
231 antiepileptic drugs, include estrogen-containing oral contraceptives, rifampin, and the protease
232 inhibitors lopinavir/ritonavir and atazanavir/ritonavir. Dosing recommendations for oral
233 contraceptives and the protease inhibitor atazanavir/ritonavir can be found in General Dosing
234 Considerations [see *Dosage and Administration (2.1)*]. Patients on rifampin and the protease
235 inhibitor lopinavir/ritonavir should follow the same dosing titration/maintenance regimen used
236 with antiepileptic drugs that induce glucuronidation and increase clearance [see *Dosage and*
237 *Administration (2.1)*, *Drug Interactions (7)*, and *Clinical Pharmacology (12.3)*].
238

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 11

239 **Table 3. The Initial Weight-Based Dosing Guide for Patients Aged 2 to 12 Years Taking**
240 **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- 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

241

242 Usual Adjunctive Maintenance Dose for Epilepsy: The usual maintenance doses
243 identified in Tables 1 and 2 are derived from dosing regimens employed in the
244 placebo-controlled adjunctive trials in which the efficacy of LAMICTAL was established. In
245 patients receiving multidrug regimens employing carbamazepine, phenytoin, phenobarbital, or
246 primidone **without valproate**, maintenance doses of adjunctive LAMICTAL as high as
247 700 mg/day have been used. In patients receiving **valproate alone**, maintenance doses of
248 adjunctive LAMICTAL as high as 200 mg/day have been used. The advantage of using doses
249 above those recommended in Tables 1-4 has not been established in controlled trials.

250 **2.3 Epilepsy—Conversion From Adjunctive Therapy to Monotherapy**

251 The goal of the transition regimen is to attempt to maintain seizure control while
252 mitigating the risk of serious rash associated with the rapid titration of LAMICTAL.

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

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

257 Conversion From Adjunctive Therapy With Carbamazepine, Phenytoin,
258 Phenobarbital, or Primidone to Monotherapy With LAMICTAL: After achieving a dose of
259 500 mg/day of LAMICTAL using the guidelines in Table 1, the concomitant enzyme-inducing
260 AED should be withdrawn by 20% decrements each week over a 4-week period. The regimen for
261 the withdrawal of the concomitant AED is based on experience gained in the controlled
262 monotherapy clinical trial.

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

265

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 12

266 **Table 4. Conversion From Adjunctive Therapy With Valproate to Monotherapy With**
267 **LAMICTAL in Patients Aged 16 Years and Older With Epilepsy**

	LAMICTAL	Valproate
Step 1	Achieve a dose of 200 mg/day according to guidelines in Table 1.	Maintain established stable dose.
Step 2	Maintain at 200 mg/day.	Decrease dose by decrements no greater than 500 mg/day/week to 500 mg/day and then maintain 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.

268

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

274 **2.4 Bipolar Disorder**

275 The goal of maintenance treatment with LAMICTAL is to delay the time to occurrence of
276 mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute
277 mood episodes with standard therapy. The target dose of LAMICTAL is 200 mg/day
278 (100 mg/day in patients taking valproate, which decreases the apparent clearance of lamotrigine,
279 and 400 mg/day in patients not taking valproate and taking either carbamazepine, phenytoin,
280 phenobarbital, primidone, or other drugs such as rifampin and the protease inhibitor
281 lopinavir/ritonavir that increase the apparent clearance of lamotrigine). In the clinical trials,
282 doses up to 400 mg/day as monotherapy were evaluated; however, no additional benefit was seen
283 at 400 mg/day compared with 200 mg/day [see *Clinical Studies (14.2)*]. Accordingly, doses
284 above 200 mg/day are not recommended. Treatment with LAMICTAL is introduced, based on
285 concurrent medications, according to the regimen outlined in Table 5. If other psychotropic
286 medications are withdrawn following stabilization, the dose of LAMICTAL should be adjusted.
287 For patients discontinuing valproate, the dose of LAMICTAL should be doubled over a 2-week
288 period in equal weekly increments (see Table 6). For patients discontinuing carbamazepine,
289 phenytoin, phenobarbital, primidone, or other drugs such as rifampin and the protease inhibitors
290 lopinavir/ritonavir and atazanavir/ritonavir that induce lamotrigine glucuronidation, the dose of
291 LAMICTAL should remain constant for the first week and then should be decreased by half over
292 a 2-week period in equal weekly decrements (see Table 6). The dose of LAMICTAL may then
293 be further adjusted to the target dose (200 mg) as clinically indicated.

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 13

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

297 To avoid an increased risk of rash, the recommended initial dose and subsequent dose
298 escalations of LAMICTAL should not be exceeded [see *Boxed Warning*].
299

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

	In Patients TAKING Valproate^a	In Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone,^b or Valproate^a	In Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone^b and NOT TAKING Valproate^a
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

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

303 ^b Drugs that induce lamotrigine glucuronidation and increase clearance, other than the
304 specified antiepileptic drugs, include estrogen-containing oral contraceptives, rifampin, and
305 the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir. Dosing
306 recommendations for oral contraceptives and the protease inhibitor atazanavir/ritonavir can
307 be found in General Dosing Considerations [see *Dosage and Administration (2.1)*]. Patients
308 on rifampin and the protease inhibitor lopinavir/ritonavir should follow the same dosing
309 titration/maintenance regimen used with antiepileptic drugs that induce glucuronidation and
310 increase clearance [see *Dosage and Administration (2.1)*, *Drug Interactions (7)*, and
311 *Clinical Pharmacology (12.3)*].
312

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 14

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

	Discontinuation of Psychotropic Drugs (excluding Valproate, ^a Carbamazepine, Phenytoin, Phenobarbital, or Primidone ^b)	After Discontinuation of Valproate ^a	After Discontinuation of Carbamazepine, Phenytoin, Phenobarbital, or Primidone ^b
		Current dose of LAMICTAL (mg/day) 100	Current dose of LAMICTAL (mg/day) 400
Week 1	Maintain current dose of LAMICTAL	150	400
Week 2	Maintain current dose of LAMICTAL	200	300
Week 3 onward	Maintain current dose of LAMICTAL	200	200

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

317 ^b Drugs that induce lamotrigine glucuronidation and increase clearance, other than the specified
318 antiepileptic drugs, include estrogen-containing oral contraceptives, rifampin, and the protease
319 inhibitors lopinavir/ritonavir and atazanavir/ritonavir. Dosing recommendations for oral
320 contraceptives and the protease inhibitor atazanavir/ritonavir can be found in General Dosing
321 Considerations [*see Dosage and Administration (2.1)*]. Patients on rifampin and the protease
322 inhibitor lopinavir/ritonavir should follow the same dosing titration/maintenance regimen used
323 with antiepileptic drugs that induce glucuronidation and increase clearance [*see Dosage and*
324 *Administration (2.1), Drug Interactions (7), and Clinical Pharmacology (12.3)*].

325

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

331 **2.5 Administration of LAMICTAL Chewable Dispersible Tablets**

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

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

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 15

339 **2.6 Administration of LAMICTAL ODT Orally Disintegrating Tablets**

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

343 **3 DOSAGE FORMS AND STRENGTHS**

344 **3.1 Tablets**

345 25 mg, white, scored, shield-shaped tablets debossed with “LAMICTAL” and “25.”

346 100 mg, peach, scored, shield-shaped tablets debossed with “LAMICTAL” and “100.”

347 150 mg, cream, scored, shield-shaped tablets debossed with “LAMICTAL” and “150.”

348 200 mg, blue, scored, shield-shaped tablets debossed with “LAMICTAL” and “200.”

349 **3.2 Chewable Dispersible Tablets**

350 2 mg, white to off-white, round tablets debossed with “LTG” over “2.”

351 5 mg, white to off-white, caplet-shaped tablets debossed with “GX CL2.”

352 25 mg, white, super elliptical-shaped tablets debossed with “GX CL5.”

353 **3.3 Orally Disintegrating Tablets**

354 25 mg, white to off-white, round, flat-faced, radius-edged tablets debossed with “LMT”
355 on one side and “25” on the other side.

356 50 mg, white to off-white, round, flat-faced, radius-edged tablets debossed with “LMT”
357 on one side and “50” on the other side.

358 100 mg, white to off-white, round, flat-faced, radius-edged tablets debossed with
359 “LAMICTAL” on one side and “100” on the other side.

360 200 mg, white to off-white, round, flat-faced, radius-edged tablets debossed with
361 “LAMICTAL” on one side and “200” on the other side.

362 **3.4 Potential Medication Errors**

363 Patients should be strongly advised to visually inspect their tablets to verify that they are
364 receiving LAMICTAL, as opposed to other medications, and that they are receiving the correct
365 formulation of lamotrigine each time they fill their prescription. Depictions of the LAMICTAL
366 Tablets, Chewable Dispersible Tablets, and Orally Disintegrating Tablets can be found in the
367 Medication Guide.

368 **4 CONTRAINDICATIONS**

369 LAMICTAL is contraindicated in patients who have demonstrated hypersensitivity (e.g.,
370 rash, angioedema, acute urticaria, extensive pruritus, mucosal ulceration) to the drug or its
371 ingredients [see Boxed Warning, Warnings and Precautions (5.1, 5.2)].

372 **5 WARNINGS AND PRECAUTIONS**

373 **5.1 Serious Skin Rashes [see Boxed Warning]**

374 Pediatric Population: The incidence of serious rash associated with hospitalization and
375 discontinuation of LAMICTAL in a prospectively followed cohort of pediatric patients (aged 2

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 16

376 to 16 years) with epilepsy receiving adjunctive therapy was approximately 0.8% (16 of 1,983).
377 When 14 of these cases were reviewed by 3 expert dermatologists, there was considerable
378 disagreement as to their proper classification. To illustrate, one dermatologist considered none of
379 the cases to be Stevens-Johnson syndrome; another assigned 7 of the 14 to this diagnosis. There
380 was 1 rash-related death in this 1,983-patient cohort. Additionally, there have been rare cases of
381 toxic epidermal necrolysis with and without permanent sequelae and/or death in US and foreign
382 postmarketing experience.

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

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

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

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

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

407 **5.2 Multiorgan Hypersensitivity Reactions and Organ Failure**

408 Multiorgan hypersensitivity reactions, also known as drug reaction with eosinophilia and
409 systemic symptoms (DRESS), have occurred with lamotrigine. Some have been fatal or life
410 threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or
411 lymphadenopathy in association with other organ system involvement, such as hepatitis,
412 nephritis, hematologic abnormalities, myocarditis, or myositis, sometimes resembling an acute
413 viral infection. Eosinophilia is often present. This disorder is variable in its expression, and other
414 organ systems not noted here may be involved.

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 17

415 Fatalities associated with acute multiorgan failure and various degrees of hepatic failure
416 have been reported in 2 of 3,796 adult patients and 4 of 2,435 pediatric patients who received
417 lamotrigine in epilepsy clinical trials. Rare fatalities from multiorgan failure have also been
418 reported in postmarketing use.

419 Isolated liver failure without rash or involvement of other organs has also been reported
420 with lamotrigine.

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

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

429 **5.3 Blood Dyscrasias**

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

434 **5.4 Suicidal Behavior and Ideation**

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

439 Pooled analyses of 199 placebo-controlled clinical trials (monotherapy and adjunctive
440 therapy) of 11 different AEDs showed that patients randomized to 1 of the AEDs had
441 approximately twice the risk (adjusted Relative Risk 1.8, 95% CI: 1.2, 2.7) of suicidal thinking
442 or behavior compared with patients randomized to placebo. In these trials, which had a median
443 treatment duration of 12 weeks, the estimated incidence of suicidal behavior or ideation among
444 27,863 AED-treated patients was 0.43%, compared with 0.24% among 16,029 placebo-treated
445 patients, representing an increase of approximately 1 case of suicidal thinking or behavior for
446 every 530 patients treated. There were 4 suicides in drug-treated patients in the trials and none in
447 placebo-treated patients, but the number of events is too small to allow any conclusion about
448 drug effect on suicide.

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

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 18

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

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

458

459 **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

460

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

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

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

475 **5.5 Use in Patients With Bipolar Disorder**

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

478 Children and Adolescents (younger than 18 years): Safety and effectiveness of
479 LAMICTAL in patients younger than 18 years with mood disorders have not been established
480 [see Warnings and Precautions (5.4)].

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 19

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

487 In addition, patients with a history of suicidal behavior or thoughts, those patients
488 exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and
489 young adults are at an increased risk of suicidal thoughts or suicide attempts and should receive
490 careful monitoring during treatment [*see Warnings and Precautions (5.4)*].

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

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

499 **5.6 Aseptic Meningitis**

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

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

513 Cerebrospinal fluid (CSF) analyzed at the time of clinical presentation in reported cases
514 was characterized by a mild to moderate pleocytosis, normal glucose levels, and mild to
515 moderate increase in protein. CSF white blood cell count differentials showed a predominance of
516 neutrophils in a majority of the cases, although a predominance of lymphocytes was reported in
517 approximately one third of the cases. Some patients also had new onset of signs and symptoms
518 of involvement of other organs (predominantly hepatic and renal involvement), which may

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 20

519 suggest that in these cases the aseptic meningitis observed was part of a hypersensitivity reaction
520 [see *Warnings and Precautions (5.2)*].

521 **5.7 Potential Medication Errors**

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

533 **5.8 Concomitant Use With Oral Contraceptives**

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

541 **5.9 Withdrawal Seizures**

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

549 **5.10 Status Epilepticus**

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

556 **5.11 Sudden Unexplained Death in Epilepsy (SUDEP)**

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 21

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

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

574 **5.12 Addition of LAMICTAL to a Multidrug Regimen That Includes Valproate**

575 Because valproate reduces the clearance of lamotrigine, the dosage of lamotrigine in the
576 presence of valproate is less than half of that required in its absence [*see Dosage and*
577 *Administration (2.2, 2.3, 2.4), Drug Interactions (7)*].

578 **5.13 Binding in the Eye and Other Melanin-Containing Tissues**

579 Because lamotrigine binds to melanin, it could accumulate in melanin-rich tissues over
580 time. This raises the possibility that lamotrigine may cause toxicity in these tissues after
581 extended use. Although ophthalmological testing was performed in 1 controlled clinical trial, the
582 testing was inadequate to exclude subtle effects or injury occurring after long-term exposure.
583 Moreover, the capacity of available tests to detect potentially adverse consequences, if any, of
584 lamotrigine's binding to melanin is unknown [*see Clinical Pharmacology (12.2)*].

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

588 **5.14 Laboratory Tests**

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

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 22

595 **6 ADVERSE REACTIONS**

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

- 598 • Serious skin rashes [see *Warnings and Precautions (5.1)*]
- 599 • Multiorgan hypersensitivity reactions and organ failure [see *Warnings and Precautions (5.2)*]
- 600 • Blood dyscrasias [see *Warnings and Precautions (5.3)*]
- 601 • Suicidal behavior and ideation [see *Warnings and Precautions (5.4)*]
- 602 • Aseptic meningitis [see *Warnings and Precautions (5.6)*]
- 603 • Withdrawal seizures [see *Warnings and Precautions (5.9)*]
- 604 • Status epilepticus [see *Warnings and Precautions (5.10)*]
- 605 • Sudden unexplained death in epilepsy [see *Warnings and Precautions (5.11)*]

606 **6.1 Clinical Trial Experience**

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

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

614 ***Epilepsy: Most Common Adverse Reactions in All Clinical Trials: Adjunctive***
615 ***Therapy in Adults With Epilepsy:*** The most commonly observed ($\geq 5\%$ for LAMICTAL and
616 more common on drug than placebo) adverse reactions seen in association with LAMICTAL
617 during adjunctive therapy in adults and not seen at an equivalent frequency among placebo-
618 treated patients were: dizziness, ataxia, somnolence, headache, diplopia, blurred vision, nausea,
619 vomiting, and rash. Dizziness, diplopia, ataxia, blurred vision, nausea, and vomiting were dose
620 related. Dizziness, diplopia, ataxia, and blurred vision occurred more commonly in patients
621 receiving carbamazepine with LAMICTAL than in patients receiving other AEDs with
622 LAMICTAL. Clinical data suggest a higher incidence of rash, including serious rash, in patients
623 receiving concomitant valproate than in patients not receiving valproate [see *Warnings and*
624 *Precautions (5.1)*].

625 Approximately 11% of the 3,378 adult patients who received LAMICTAL as adjunctive
626 therapy in premarketing clinical trials discontinued treatment because of an adverse reaction. The
627 adverse reactions most commonly associated with discontinuation were rash (3.0%), dizziness
628 (2.8%), and headache (2.5%).

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

631 ***Monotherapy in Adults With Epilepsy:*** The most commonly observed ($\geq 5\%$ for
632 LAMICTAL and more common on drug than placebo) adverse reactions seen in association with
633 the use of LAMICTAL during the monotherapy phase of the controlled trial in adults not seen at

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 23

634 an equivalent rate in the control group were vomiting, coordination abnormality, dyspepsia,
635 nausea, dizziness, rhinitis, anxiety, insomnia, infection, pain, weight decrease, chest pain, and
636 dysmenorrhea. The most commonly observed ($\geq 5\%$ for LAMICTAL and more common on drug
637 than placebo) adverse reactions associated with the use of LAMICTAL during the conversion to
638 monotherapy (add-on) period, not seen at an equivalent frequency among low-dose valproate-
639 treated patients, were dizziness, headache, nausea, asthenia, coordination abnormality, vomiting,
640 rash, somnolence, diplopia, ataxia, accidental injury, tremor, blurred vision, insomnia,
641 nystagmus, diarrhea, lymphadenopathy, pruritus, and sinusitis.

642 Approximately 10% of the 420 adult patients who received LAMICTAL as monotherapy
643 in premarketing clinical trials discontinued treatment because of an adverse reaction. The
644 adverse reactions most commonly associated with discontinuation were rash (4.5%), headache
645 (3.1%), and asthenia (2.4%).

646 *Adjunctive Therapy in Pediatric Patients With Epilepsy:* The most commonly
647 observed ($\geq 5\%$ for LAMICTAL and more common on drug than placebo) adverse reactions seen
648 in association with the use of LAMICTAL as adjunctive treatment in pediatric patients aged 2 to
649 16 years and not seen at an equivalent rate in the control group were infection, vomiting, rash,
650 fever, somnolence, accidental injury, dizziness, diarrhea, abdominal pain, nausea, ataxia, tremor,
651 asthenia, bronchitis, flu syndrome, and diplopia.

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

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

660 *Controlled Adjunctive Clinical Trials in Adults With Epilepsy:* Table 8 lists
661 treatment-emergent adverse reactions that occurred in at least 2% of adult patients with epilepsy
662 treated with LAMICTAL in placebo-controlled trials and were numerically more frequent in the
663 patients treated with LAMICTAL. In these trials, either LAMICTAL or placebo was added to the
664 patient's current AED therapy. Adverse reactions were usually mild to moderate in intensity.
665

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 24

666 **Table 8. Treatment-Emergent Adverse Reaction Incidence in Placebo-Controlled**
667 **Adjunctive Trials in Adult Patients With Epilepsy^a (Adverse reactions in at least 2% of**
668 **patients treated with LAMICTAL and numerically more frequent than in the placebo**
669 **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-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 25

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

670 ^a Patients in these adjunctive trials were receiving 1 to 3 of the concomitant antiepileptic drugs
671 carbamazepine, phenytoin, phenobarbital, or primidone in addition to LAMICTAL or
672 placebo. Patients may have reported multiple adverse reactions during the trial or at
673 discontinuation; thus, patients may be included in more than 1 category.
674

675 In a randomized, parallel trial comparing placebo with 300 and 500 mg/day of
676 LAMICTAL, some of the more common drug-related adverse reactions were dose related (see
677 Table 9).
678

679 **Table 9. Dose-Related Adverse Reactions From a Randomized, Placebo-Controlled,**
680 **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 ^{a,b}
Blurred vision	10	11	25 ^{a,b}
Diplopia	8	24 ^a	49 ^{a,b}
Dizziness	27	31	54 ^{a,b}
Nausea	11	18	25 ^a
Vomiting	4	11	18 ^a

681 ^a Significantly greater than placebo group ($P < 0.05$).

682 ^b Significantly greater than group receiving LAMICTAL 300 mg ($P < 0.05$).

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 26

683

684 The overall adverse reaction profile for LAMICTAL was similar between females and
685 males and was independent of age. Because the largest non-Caucasian racial subgroup was only
686 6% of patients exposed to LAMICTAL in placebo-controlled trials, there are insufficient data to
687 support a statement regarding the distribution of adverse reaction reports by race. Generally,
688 females receiving either LAMICTAL as adjunctive therapy or placebo were more likely to report
689 adverse reactions than males. The only adverse reaction for which the reports on LAMICTAL
690 were greater than 10% more frequent in females than males (without a corresponding difference
691 by gender on placebo) was dizziness (difference = 16.5%). There was little difference between
692 females and males in the rates of discontinuation of LAMICTAL for individual adverse
693 reactions.

694 *Controlled Monotherapy Trial in Adults With Partial-Onset Seizures:* Table
695 10 lists treatment-emergent adverse reactions that occurred in at least 5% of patients with
696 epilepsy treated with monotherapy with LAMICTAL in a double-blind trial following
697 discontinuation of either concomitant carbamazepine or phenytoin not seen at an equivalent
698 frequency in the control group.

699

700 **Table 10. Treatment-Emergent Adverse Reaction Incidence in a Controlled**
701 **Monotherapy Trial in Adult Patients With Partial-Onset Seizures^a (Adverse reactions in**
702 **at least 5% of patients treated with LAMICTAL and numerically more frequent than in**
703 **the valproate group.)**

Body System/ Adverse Reaction	Percent of Patients Receiving LAMICTAL ^b as Monotherapy (n = 43)	Percent of Patients Receiving Low-Dose Valproate ^c Monotherapy (n = 44)
Body as a whole		
Pain	5	0
Infection	5	2
Chest pain	5	2
Digestive		
Vomiting	9	0
Dyspepsia	7	2
Nausea	7	2
Metabolic and nutritional		
Weight decrease	5	2
Nervous		
Coordination abnormality	7	0
Dizziness	7	0
Anxiety	5	0

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 27

Insomnia	5	2
Respiratory Rhinitis	7	2
Urogenital (female patients only)	(n = 21)	(n = 28)
Dysmenorrhea	5	0

704 ^a Patients in this trial were converted to LAMICTAL or valproate monotherapy from
705 adjunctive therapy with carbamazepine or phenytoin. Patients may have reported multiple
706 adverse reactions during the trial; thus, patients may be included in more than 1 category.

707 ^b Up to 500 mg/day.

708 ^c 1,000 mg/day.

709

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

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

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

714 *Metabolic and Nutritional:* Peripheral edema.

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

717 *Respiratory:* Epistaxis, bronchitis, dyspnea.

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

719 *Special Senses:* Vision abnormality.

720

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

725

726 **Table 11. Treatment-Emergent Adverse Reaction Incidence in Placebo-Controlled**
727 **Adjunctive Trials in Pediatric Patients With Epilepsy (Adverse reactions in at least**
728 **2% of patients treated with LAMICTAL and numerically more frequent than in the**
729 **placebo group.)**

Body System/Adverse Reaction	Percent of Patients Receiving LAMICTAL (n = 168)	Percent of Patients Receiving Placebo (n = 171)
Body as a whole		
Infection	20	17
Fever	15	14
Accidental injury	14	12

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 28

Abdominal pain	10	5
Asthenia	8	4
Flu syndrome	7	6
Pain	5	4
Facial edema	2	1
Photosensitivity	2	0
Cardiovascular		
Hemorrhage	2	1
Digestive		
Vomiting	20	16
Diarrhea	11	9
Nausea	10	2
Constipation	4	2
Dyspepsia	2	1
Hemic and lymphatic		
Lymphadenopathy	2	1
Metabolic and nutritional		
Edema	2	0
Nervous system		
Somnolence	17	15
Dizziness	14	4
Ataxia	11	3
Tremor	10	1
Emotional lability	4	2
Gait abnormality	4	2
Thinking abnormality	3	2
Convulsions	2	1
Nervousness	2	1
Vertigo	2	1
Respiratory		
Pharyngitis	14	11
Bronchitis	7	5
Increased cough	7	6
Sinusitis	2	1
Bronchospasm	2	1
Skin		
Rash	14	12
Eczema	2	1
Pruritus	2	1

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 29

Special senses		
Diplopia	5	1
Blurred vision	4	1
Visual abnormality	2	0
Urogenital		
Male and female patients		
Urinary tract infection	3	0

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

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

749

750

751

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

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 30

752 **Table 12. Treatment-Emergent Adverse Reaction Incidence in 2 Placebo-Controlled Trials**
753 **in Adult Patients With Bipolar I Disorder^a (Adverse reactions in at least 5% of patients**
754 **treated with LAMICTAL as monotherapy and numerically more frequent than in the**
755 **placebo group.)**

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

756 ^a Patients in these trials were converted to LAMICTAL (100 to 400 mg/day) or placebo
757 monotherapy from add-on therapy with other psychotropic medications. Patients may have
758 reported multiple adverse reactions during the trial; thus, patients may be included in more
759 than 1 category.

760 ^b In the overall bipolar and other mood disorders clinical trials, the rate of serious rash was
761 0.08% (1 of 1,233) of adult patients who received LAMICTAL as initial monotherapy and
762 0.13% (2 of 1,538) of adult patients who received LAMICTAL as adjunctive therapy [*see*
763 *Warnings and Precautions (5.1)*].

764
765 These adverse reactions were usually mild to moderate in intensity. Other reactions that
766 occurred in 5% or more patients but equally or more frequently in the placebo group included:
767 dizziness, mania, headache, infection, influenza, pain, accidental injury, diarrhea, and dyspepsia.

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

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 31

770 *General:* Fever, neck pain.

771 *Cardiovascular:* Migraine.

772 *Digestive:* Flatulence.

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

774 *Musculoskeletal:* Arthralgia, myalgia.

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

777 *Respiratory:* Sinusitis.

778 *Urogenital:* Urinary frequency.

779 *Adverse Reactions Following Abrupt Discontinuation:* In the 2 maintenance trials,
780 there was no increase in the incidence, severity, or type of adverse reactions in patients with
781 bipolar disorder after abruptly terminating therapy with LAMICTAL. In clinical trials in patients
782 with bipolar disorder, 2 patients experienced seizures shortly after abrupt withdrawal of
783 LAMICTAL. However, there were confounding factors that may have contributed to the
784 occurrence of seizures in these patients with bipolar disorder [see *Warnings and Precautions*
785 (5.9)].

786 *Mania/Hypomania/Mixed Episodes:* During the double-blind, placebo-controlled
787 clinical trials in bipolar I disorder in which patients were converted to monotherapy with
788 LAMICTAL (100 to 400 mg/day) from other psychotropic medications and followed for up to
789 18 months, the rates of manic or hypomanic or mixed mood episodes reported as adverse
790 reactions were 5% for patients treated with LAMICTAL (n = 227), 4% for patients treated with
791 lithium (n = 166), and 7% for patients treated with placebo (n = 190). In all bipolar controlled
792 trials combined, adverse reactions of mania (including hypomania and mixed mood episodes)
793 were reported in 5% of patients treated with LAMICTAL (n = 956), 3% of patients treated with
794 lithium (n = 280), and 4% of patients treated with placebo (n = 803).

795 **6.2 Other Adverse Reactions Observed in All Clinical Trials**

796 LAMICTAL has been administered to 6,694 individuals for whom complete adverse
797 reaction data was captured during all clinical trials, only some of which were placebo controlled.
798 During these trials, all adverse reactions were recorded by the clinical investigators using
799 terminology of their own choosing. To provide a meaningful estimate of the proportion of
800 individuals having adverse reactions, similar types of adverse reactions were grouped into a
801 smaller number of standardized categories using modified COSTART dictionary terminology.
802 The frequencies presented represent the proportion of the 6,694 individuals exposed to
803 LAMICTAL who experienced an event of the type cited on at least 1 occasion while receiving
804 LAMICTAL. All reported adverse reactions are included except those already listed in the
805 previous tables or elsewhere in the labeling, those too general to be informative, and those not
806 reasonably associated with the use of the drug.

807 Adverse reactions are further classified within body system categories and enumerated in
808 order of decreasing frequency using the following definitions: *frequent* adverse reactions are

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 32

809 defined as those occurring in at least 1/100 patients; *infrequent* adverse reactions are those
810 occurring in 1/100 to 1/1,000 patients; *rare* adverse reactions are those occurring in fewer than
811 1/1,000 patients.

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

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

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

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

823 Endocrine System: *Rare:* Goiter, hypothyroidism.

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

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

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

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

840 Respiratory System: *Infrequent:* Yawn. *Rare:* Hiccup, hyperventilation.

841 Special Senses: *Frequent:* Amblyopia. *Infrequent:* Abnormality of accommodation,
842 conjunctivitis, dry eyes, ear pain, photophobia, taste perversion, tinnitus. *Rare:* Deafness,
843 lacrimation disorder, oscillopsia, parosmia, ptosis, strabismus, taste loss, uveitis, visual field
844 defect.

845 Urogenital System: *Infrequent:* Abnormal ejaculation, hematuria, impotence,
846 menorrhagia, polyuria, urinary incontinence. *Rare:* Acute kidney failure, anorgasmia, breast

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 33

847 abscess, breast neoplasm, creatinine increase, cystitis, dysuria, epididymitis, female lactation,
848 kidney failure, kidney pain, nocturia, urinary retention, urinary urgency.

849 **6.3 Postmarketing Experience**

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

854 Blood and Lymphatic: Agranulocytosis, hemolytic anemia, lymphadenopathy not
855 associated with hypersensitivity disorder.

856 Gastrointestinal: Esophagitis.

857 Hepatobiliary Tract and Pancreas: Pancreatitis.

858 Immunologic: Lupus-like reaction, vasculitis.

859 Lower Respiratory: Apnea.

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

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

864 Non-site Specific: Progressive immunosuppression.

865 **7 DRUG INTERACTIONS**

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

869

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

Concomitant Drug	Effect on Concentration of Lamotrigine or Concomitant Drug	Clinical Comment
Estrogen-containing oral contraceptive preparations containing 30 mcg ethinylestradiol and 150 mcg levonorgestrel	↓ lamotrigine ↓ levonorgestrel	Decreased lamotrigine concentrations approximately 50%. Decrease in levonorgestrel component by 19%.
Carbamazepine and carbamazepine epoxide	↓ lamotrigine ? carbamazepine epoxide	Addition of carbamazepine decreases lamotrigine concentration approximately 40%. May increase carbamazepine epoxide levels.

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 34

Lopinavir/ritonavir	↓ lamotrigine	Decreased lamotrigine concentration approximately 50%.
Atazanavir/ritonavir	↓ lamotrigine	Decreased lamotrigine AUC approximately 32%.
Phenobarbital/primidone	↓ lamotrigine	Decreased lamotrigine concentration approximately 40%.
Phenytoin	↓ lamotrigine	Decreased lamotrigine concentration approximately 40%.
Rifampin	↓ lamotrigine	Decreased lamotrigine AUC approximately 40%.
Valproate	↑ lamotrigine ? valproate	Increased lamotrigine concentrations slightly more than 2-fold. There are conflicting study results regarding effect of lamotrigine on valproate concentrations: 1) a mean 25% decrease in valproate concentrations in healthy volunteers, 2) no change in valproate concentrations in controlled clinical trials in patients with epilepsy.

871 ↓ = Decreased (induces lamotrigine glucuronidation).

872 ↑ = Increased (inhibits lamotrigine glucuronidation).

873 ? = Conflicting data.

874 **8 USE IN SPECIFIC POPULATIONS**

875 **8.1 Pregnancy**

876 Teratogenic Effects: Pregnancy Category C. No evidence of teratogenicity was found in
877 mice, rats, or rabbits when lamotrigine was orally administered to pregnant animals during the
878 period of organogenesis at doses up to 1.2, 0.5, and 1.1 times, respectively, on a mg/m² basis, the
879 highest usual human maintenance dose (i.e., 500 mg/day). However, maternal toxicity and
880 secondary fetal toxicity producing reduced fetal weight and/or delayed ossification were seen in
881 mice and rats, but not in rabbits at these doses. Teratology studies were also conducted using
882 bolus intravenous administration of the isethionate salt of lamotrigine in rats and rabbits. In rat
883 dams administered an intravenous dose at 0.6 times the highest usual human maintenance dose,
884 the incidence of intrauterine death without signs of teratogenicity was increased.

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

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 35

889 was increased in offspring of dams receiving 25 mg/kg/day. These doses represent 0.1 and 0.5
890 times the clinical dose on a mg/m² basis, respectively.

891 Lamotrigine did not affect fertility, teratogenesis, or postnatal development when rats
892 were dosed prior to and during mating, and throughout gestation and lactation at doses
893 equivalent to 0.4 times the highest usual human maintenance dose on a mg/m² basis.

894 When pregnant rats were orally dosed at 0.1, 0.14, or 0.3 times the highest human
895 maintenance dose (on a mg/m² basis) during the latter part of gestation (days 15 to 20), maternal
896 toxicity and fetal death were seen. In dams, food consumption and weight gain were reduced,
897 and the gestation period was slightly prolonged (22.6 vs. 22.0 days in the control group).
898 Stillborn pups were found in all 3 drug-treated groups, with the highest number in the high-dose
899 group. Postnatal death was also seen, but only in the 2 highest doses, and occurred between days
900 1 and 20. Some of these deaths appear to be drug related and not secondary to the maternal
901 toxicity. A no-observed-effect level (NOEL) could not be determined for this study.

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

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

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

919 **8.2 Labor and Delivery**

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

921 **8.3 Nursing Mothers**

922 Lamotrigine is present in milk from lactating women taking LAMICTAL. Data from
923 multiple small studies indicate that lamotrigine plasma levels in human milk-fed infants have
924 been reported to be as high as 50% of the maternal serum levels. Neonates and young infants are
925 at risk for high serum levels because maternal serum and milk levels can rise to high levels
926 postpartum if lamotrigine dosage has been increased during pregnancy but not later reduced to
927 the pre-pregnancy dosage. Lamotrigine exposure is further increased due to the immaturity of the

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 36

928 infant glucuronidation capacity needed for drug clearance. Events including apnea, drowsiness,
929 and poor sucking have been reported in infants who have been human milk-fed by mothers using
930 lamotrigine; whether or not these events were caused by lamotrigine is unknown. Human milk-
931 fed infants should be closely monitored for adverse events resulting from lamotrigine.
932 Measurement of infant serum levels should be performed to rule out toxicity if concerns arise.
933 Human milk-feeding should be discontinued in infants with lamotrigine toxicity. Caution should
934 be exercised when LAMICTAL is administered to a nursing woman.

935 **8.4 Pediatric Use**

936 LAMICTAL is indicated for adjunctive therapy in patients aged 2 years and older for
937 partial-onset seizures, the generalized seizures of Lennox-Gastaut syndrome, and PGTC seizures.

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

946 Safety and effectiveness in patients younger than 18 years with bipolar disorder have not
947 been established.

948 **8.5 Geriatric Use**

949 Clinical trials of LAMICTAL for epilepsy and bipolar disorder did not include sufficient
950 numbers of patients aged 65 years and older to determine whether they respond differently from
951 younger patients or exhibit a different safety profile than that of younger patients. In general,
952 dose selection for an elderly patient should be cautious, usually starting at the low end of the
953 dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and
954 of concomitant disease or other drug therapy.

955 **8.6 Patients With Hepatic Impairment**

956 Experience in patients with hepatic impairment is limited. Based on a clinical
957 pharmacology study in 24 subjects with mild, moderate, and severe liver impairment [*see*
958 *Clinical Pharmacology (12.3)*], the following general recommendations can be made. No dosage
959 adjustment is needed in patients with mild liver impairment. Initial, escalation, and maintenance
960 doses should generally be reduced by approximately 25% in patients with moderate and severe
961 liver impairment without ascites and 50% in patients with severe liver impairment with ascites.
962 Escalation and maintenance doses may be adjusted according to clinical response [*see Dosage*
963 *and Administration (2.1)*].

964 **8.7 Patients With Renal Impairment**

965 Lamotrigine is metabolized mainly by glucuronic acid conjugation, with the majority of
966 the metabolites being recovered in the urine. In a small study comparing a single dose of

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 37

967 lamotrigine in subjects with varying degrees of renal impairment with healthy volunteers, the
968 plasma half-life of lamotrigine was approximately twice as long in the subjects with chronic
969 renal failure [see *Clinical Pharmacology (12.3)*].

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

975 **10 OVERDOSAGE**

976 **10.1 Human Overdose Experience**

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

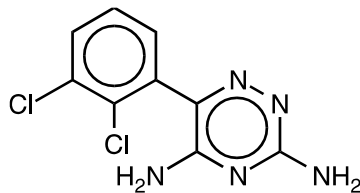
980 **10.2 Management of Overdose**

981 There are no specific antidotes for lamotrigine. Following a suspected overdose,
982 hospitalization of the patient is advised. General supportive care is indicated, including frequent
983 monitoring of vital signs and close observation of the patient. If indicated, emesis should be
984 induced; usual precautions should be taken to protect the airway. It should be kept in mind that
985 immediate-release lamotrigine is rapidly absorbed [see *Clinical Pharmacology (12.3)*]. It is
986 uncertain whether hemodialysis is an effective means of removing lamotrigine from the blood. In
987 6 renal failure patients, about 20% of the amount of lamotrigine in the body was removed by
988 hemodialysis during a 4-hour session. A Poison Control Center should be contacted for
989 information on the management of overdosage of LAMICTAL.

990 **11 DESCRIPTION**

991 LAMICTAL (lamotrigine), an AED of the phenyltriazine class, is chemically unrelated to
992 existing AEDs. Lamotrigine's chemical name is 3,5-diamino-6-(2,3-dichlorophenyl)-as-triazine,
993 its molecular formula is $C_9H_7N_5Cl_2$, and its molecular weight is 256.09. Lamotrigine is a white to
994 pale cream-colored powder and has a pK_a of 5.7. Lamotrigine is very slightly soluble in water
995 (0.17 mg/mL at 25°C) and slightly soluble in 0.1 M HCl (4.1 mg/mL at 25°C). The structural
996 formula is:

997



998

999

1000 LAMICTAL Tablets are supplied for oral administration as 25-mg (white), 100-mg
1001 (peach), 150-mg (cream), and 200-mg (blue) tablets. Each tablet contains the labeled amount of

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 38

1002 lamotrigine and the following inactive ingredients: lactose; magnesium stearate; microcrystalline
1003 cellulose; povidone; sodium starch glycolate; FD&C Yellow No. 6 Lake (100-mg tablet only);
1004 ferric oxide, yellow (150-mg tablet only); and FD&C Blue No. 2 Lake (200-mg tablet only).

1005 LAMICTAL Chewable Dispersible Tablets are supplied for oral administration. The
1006 tablets contain 2 mg (white), 5 mg (white), or 25 mg (white) of lamotrigine and the following
1007 inactive ingredients: blackcurrant flavor, calcium carbonate, low-substituted
1008 hydroxypropylcellulose, magnesium aluminum silicate, magnesium stearate, povidone, saccharin
1009 sodium, and sodium starch glycolate.

1010 LAMICTAL ODT Orally Disintegrating Tablets are supplied for oral administration. The
1011 tablets contain 25 mg (white to off-white), 50 mg (white to off-white), 100 mg (white to
1012 off-white), or 200 mg (white to off-white) of lamotrigine and the following inactive ingredients:
1013 artificial cherry flavor, crospovidone, ethylcellulose, magnesium stearate, mannitol,
1014 polyethylene, and sucralose.

1015 LAMICTAL ODT Orally Disintegrating Tablets are formulated using technologies
1016 (Microcaps[®] and AdvaTab[®]) designed to mask the bitter taste of lamotrigine and achieve a rapid
1017 dissolution profile. Tablet characteristics including flavor, mouth-feel, after-taste, and ease of use
1018 were rated as favorable in a study in 108 healthy volunteers.

1019 **12 CLINICAL PHARMACOLOGY**

1020 **12.1 Mechanism of Action**

1021 The precise mechanism(s) by which lamotrigine exerts its anticonvulsant action are
1022 unknown. In animal models designed to detect anticonvulsant activity, lamotrigine was effective
1023 in preventing seizure spread in the maximum electroshock (MES) and pentylenetetrazol (scMet)
1024 tests, and prevented seizures in the visually and electrically evoked after-discharge (EEAD) tests
1025 for antiepileptic activity. Lamotrigine also displayed inhibitory properties in the kindling model
1026 in rats both during kindling development and in the fully kindled state. The relevance of these
1027 models to human epilepsy, however, is not known.

1028 One proposed mechanism of action of lamotrigine, the relevance of which remains to be
1029 established in humans, involves an effect on sodium channels. In vitro pharmacological studies
1030 suggest that lamotrigine inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal
1031 membranes and consequently modulating presynaptic transmitter release of excitatory amino
1032 acids (e.g., glutamate and aspartate).

1033 Although the relevance for human use is unknown, the following data characterize the
1034 performance of lamotrigine in receptor binding assays. Lamotrigine had a weak inhibitory effect
1035 on the serotonin 5-HT₃ receptor (IC₅₀ = 18 μM). It does not exhibit high affinity binding
1036 (IC₅₀>100 μM) to the following neurotransmitter receptors: adenosine A₁ and A₂; adrenergic α₁,
1037 α₂, and β; dopamine D₁ and D₂; γ-aminobutyric acid (GABA) A and B; histamine H₁; kappa
1038 opioid; muscarinic acetylcholine; and serotonin 5-HT₂. Studies have failed to detect an effect of
1039 lamotrigine on dihydropyridine-sensitive calcium channels. It had weak effects at sigma opioid

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 39

1040 receptors ($IC_{50} = 145 \mu M$). Lamotrigine did not inhibit the uptake of norepinephrine, dopamine,
1041 or serotonin ($IC_{50} > 200 \mu M$) when tested in rat synaptosomes and/or human platelets in vitro.

1042 **Effect of Lamotrigine on N-Methyl d-Aspartate-Receptor Mediated Activity:**

1043 Lamotrigine did not inhibit N-methyl d-aspartate (NMDA)-induced depolarizations in rat cortical
1044 slices or NMDA-induced cyclic GMP formation in immature rat cerebellum, nor did lamotrigine
1045 displace compounds that are either competitive or noncompetitive ligands at this glutamate
1046 receptor complex (CNQX, CGS, TCHP). The IC_{50} for lamotrigine effects on NMDA-induced
1047 currents (in the presence of $3 \mu M$ of glycine) in cultured hippocampal neurons exceeded 100
1048 μM .

1049 The mechanisms by which lamotrigine exerts its therapeutic action in bipolar disorder
1050 have not been established.

1051 **12.2 Pharmacodynamics**

1052 **Folate Metabolism:** In vitro, lamotrigine inhibited dihydrofolate reductase, the enzyme
1053 that catalyzes the reduction of dihydrofolate to tetrahydrofolate. Inhibition of this enzyme may
1054 interfere with the biosynthesis of nucleic acids and proteins. When oral daily doses of
1055 lamotrigine were given to pregnant rats during organogenesis, fetal, placental, and maternal
1056 folate concentrations were reduced. Significantly reduced concentrations of folate are associated
1057 with teratogenesis [see *Use in Specific Populations (8.1)*]. Folate concentrations were also
1058 reduced in male rats given repeated oral doses of lamotrigine. Reduced concentrations were
1059 partially returned to normal when supplemented with folic acid.

1060 **Accumulation in Kidneys:** Lamotrigine accumulated in the kidney of the male rat,
1061 causing chronic progressive nephrosis, necrosis, and mineralization. These findings are attributed
1062 to α -2 microglobulin, a species- and sex-specific protein that has not been detected in humans or
1063 other animal species.

1064 **Melanin Binding:** Lamotrigine binds to melanin-containing tissues, e.g., in the eye and
1065 pigmented skin. It has been found in the uveal tract up to 52 weeks after a single dose in rodents.

1066 **Cardiovascular:** In dogs, lamotrigine is extensively metabolized to a 2-N-methyl
1067 metabolite. This metabolite causes dose-dependent prolongation of the PR interval, widening of
1068 the QRS complex, and, at higher doses, complete AV conduction block. Similar cardiovascular
1069 effects are not anticipated in humans because only trace amounts of the 2-N-methyl metabolite
1070 ($< 0.6\%$ of lamotrigine dose) have been found in human urine [see *Clinical Pharmacology*
1071 *(12.3)*]. However, it is conceivable that plasma concentrations of this metabolite could be
1072 increased in patients with a reduced capacity to glucuronidate lamotrigine (e.g., in patients with
1073 liver disease, patients taking concomitant medications that inhibit glucuronidation).

1074 **12.3 Pharmacokinetics**

1075 The pharmacokinetics of lamotrigine have been studied in subjects with epilepsy, healthy
1076 young and elderly volunteers, and volunteers with chronic renal failure. Lamotrigine
1077 pharmacokinetic parameters for adult and pediatric subjects and healthy normal volunteers are
1078 summarized in Tables 14 and 16.

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 40

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Table 14. Mean Pharmacokinetic Parameters^a in Healthy Volunteers and Adult Subjects With Epilepsy

Adult Study Population	Number of Subjects	T_{max}: Time of Maximum Plasma Concentration (h)	t_{1/2}: Elimination Half-life (h)	CL/F: Apparent Plasma Clearance (mL/min/kg)
Healthy volunteers taking no other medications:				
Single-dose LAMICTAL	179	2.2 (0.25-12.0)	32.8 (14.0-103.0)	0.44 (0.12-1.10)
Multiple-dose LAMICTAL	36	1.7 (0.5-4.0)	25.4 (11.6-61.6)	0.58 (0.24-1.15)
Healthy volunteers taking valproate:				
Single-dose LAMICTAL	6	1.8 (1.0-4.0)	48.3 (31.5-88.6)	0.30 (0.14-0.42)
Multiple-dose LAMICTAL	18	1.9 (0.5-3.5)	70.3 (41.9-113.5)	0.18 (0.12-0.33)
Subjects with epilepsy taking valproate only:				
Single-dose LAMICTAL	4	4.8 (1.8-8.4)	58.8 (30.5-88.8)	0.28 (0.16-0.40)
Subjects with epilepsy taking carbamazepine, phenytoin, phenobarbital, or primidone^b plus valproate:				
Single-dose LAMICTAL	25	3.8 (1.0-10.0)	27.2 (11.2-51.6)	0.53 (0.27-1.04)
Subjects with epilepsy taking carbamazepine, phenytoin, phenobarbital, or primidone:^b				
Single-dose LAMICTAL	24	2.3 (0.5-5.0)	14.4 (6.4-30.4)	1.10 (0.51-2.22)
Multiple-dose LAMICTAL	17	2.0 (0.75-5.93)	12.6 (7.5-23.1)	1.21 (0.66-1.82)

1082

1083

^a The majority of parameter means determined in each study had coefficients of variation between 20% and 40% for half-life and CL/F and between 30% and 70% for T_{max}. The overall

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 41

1084 mean values were calculated from individual study means that were weighted based on the
1085 number of volunteers/subjects in each study. The numbers in parentheses below each
1086 parameter mean represent the range of individual volunteer/subject values across studies.
1087 ^b Carbamazepine, phenytoin, phenobarbital, and primidone have been shown to increase the
1088 apparent clearance of lamotrigine. Estrogen-containing oral contraceptives and other drugs,
1089 such as rifampin and protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir, that
1090 induce lamotrigine glucuronidation have also been shown to increase the apparent clearance
1091 of lamotrigine [*see Drug Interactions (7)*].
1092

1093 Absorption: Lamotrigine is rapidly and completely absorbed after oral administration
1094 with negligible first-pass metabolism (absolute bioavailability is 98%). The bioavailability is not
1095 affected by food. Peak plasma concentrations occur anywhere from 1.4 to 4.8 hours following
1096 drug administration. The lamotrigine chewable/dispersible tablets were found to be equivalent
1097 whether administered as dispersed in water, chewed and swallowed, or swallowed as whole, to
1098 the lamotrigine compressed tablets in terms of rate and extent of absorption. In terms of rate and
1099 extent of absorption, lamotrigine orally disintegrating tablets whether disintegrated in the mouth
1100 or swallowed whole with water were equivalent to the lamotrigine compressed tablets swallowed
1101 with water.

1102 Dose Proportionality: In healthy volunteers not receiving any other medications and
1103 given single doses, the plasma concentrations of lamotrigine increased in direct proportion to the
1104 dose administered over the range of 50 to 400 mg. In 2 small studies (n = 7 and 8) of patients
1105 with epilepsy who were maintained on other AEDs, there also was a linear relationship between
1106 dose and lamotrigine plasma concentrations at steady state following doses of 50 to 350 mg
1107 twice daily.

1108 Distribution: Estimates of the mean apparent volume of distribution (Vd/F) of
1109 lamotrigine following oral administration ranged from 0.9 to 1.3 L/kg. Vd/F is independent of
1110 dose and is similar following single and multiple doses in both patients with epilepsy and in
1111 healthy volunteers.

1112 Protein Binding: Data from in vitro studies indicate that lamotrigine is approximately
1113 55% bound to human plasma proteins at plasma lamotrigine concentrations from 1 to 10 mcg/mL
1114 (10 mcg/mL is 4 to 6 times the trough plasma concentration observed in the controlled efficacy
1115 trials). Because lamotrigine is not highly bound to plasma proteins, clinically significant
1116 interactions with other drugs through competition for protein binding sites are unlikely. The
1117 binding of lamotrigine to plasma proteins did not change in the presence of therapeutic
1118 concentrations of phenytoin, phenobarbital, or valproate. Lamotrigine did not displace other
1119 AEDs (carbamazepine, phenytoin, phenobarbital) from protein-binding sites.

1120 Metabolism: Lamotrigine is metabolized predominantly by glucuronic acid conjugation;
1121 the major metabolite is an inactive 2-N-glucuronide conjugate. After oral administration of
1122 240 mg of ¹⁴C-lamotrigine (15 μCi) to 6 healthy volunteers, 94% was recovered in the urine and

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 42

1123 2% was recovered in the feces. The radioactivity in the urine consisted of unchanged lamotrigine
1124 (10%), the 2-N-glucuronide (76%), a 5-N-glucuronide (10%), a 2-N-methyl metabolite (0.14%),
1125 and other unidentified minor metabolites (4%).

1126 **Enzyme Induction:** The effects of lamotrigine on the induction of specific families of
1127 mixed-function oxidase isozymes have not been systematically evaluated.

1128 Following multiple administrations (150 mg twice daily) to normal volunteers taking no
1129 other medications, lamotrigine induced its own metabolism, resulting in a 25% decrease in $t_{1/2}$ and
1130 a 37% increase in CL/F at steady state compared with values obtained in the same volunteers
1131 following a single dose. Evidence gathered from other sources suggests that self-induction by
1132 lamotrigine may not occur when lamotrigine is given as adjunctive therapy in patients receiving
1133 enzyme-inducing drugs such as carbamazepine, phenytoin, phenobarbital, primidone, or other
1134 drugs such as rifampin and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir
1135 that induce lamotrigine glucuronidation [see *Drug Interactions (7)*].

1136 **Elimination:** The elimination half-life and apparent clearance of lamotrigine following
1137 oral administration of LAMICTAL to adult subjects with epilepsy and healthy volunteers is
1138 summarized in Table 14. Half-life and apparent oral clearance vary depending on concomitant
1139 AEDs.

1140 **Drug Interactions:** The apparent clearance of lamotrigine is affected by the
1141 coadministration of certain medications [see *Warnings and Precautions (5.8, 5.12), Drug*
1142 *Interactions (7)*].

1143 The net effects of drug interactions with lamotrigine are summarized in Tables 13 and 15,
1144 followed by details of the drug interaction studies below.

1145
1146

Table 15. Summary of Drug Interactions With Lamotrigine

Drug	Drug Plasma Concentration With Adjunctive Lamotrigine ^a	Lamotrigine Plasma Concentration With Adjunctive Drugs ^b
Oral contraceptives (e.g., ethinylestradiol/levonorgestrel) ^c	↔ ^d	↓
Atazanavir/ritonavir	↔ ^e	↓
Bupropion	Not assessed	↔
Carbamazepine	↔	↓
Carbamazepine epoxide ^f	?	
Felbamate	Not assessed	↔
Gabapentin	Not assessed	↔
Levetiracetam	↔	↔
Lithium	↔	Not assessed
Lopinavir/ritonavir	↔ ^e	↓
Olanzapine	↔	↔ ^g

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 43

Oxcarbazepine	↔	↔
10-Monohydroxy oxcarbazepine metabolite ^h	↔	
Phenobarbital/primidone	↔	↓
Phenytoin	↔	↓
Pregabalin	↔	↔
Rifampin	Not assessed	↓
Risperidone	↔	Not assessed
9-hydroxyrisperidone ⁱ	↔	
Topiramate	↔ ^j	↔
Valproate	↓	↑
Valproate + phenytoin and/or carbamazepine	Not assessed	↔
Zonisamide	Not assessed	↔

1147 ^a From adjunctive clinical trials and volunteer trials.

1148 ^b Net effects were estimated by comparing the mean clearance values obtained in adjunctive
1149 clinical trials and volunteer trials.

1150 ^c The effect of other hormonal contraceptive preparations or hormone replacement therapy on
1151 the pharmacokinetics of lamotrigine has not been systematically evaluated in clinical trials,
1152 although the effect may be similar to that seen with the ethinylestradiol/levonorgestrel
1153 combinations.

1154 ^d Modest decrease in levonorgestrel.

1155 ^e Compared to historical controls.

1156 ^f Not administered, but an active metabolite of carbamazepine.

1157 ^g Slight decrease, not expected to be clinically relevant.

1158 ^h Not administered, but an active metabolite of oxcarbazepine.

1159 ⁱ Not administered, but an active metabolite of risperidone.

1160 ^j Slight increase, not expected to be clinically relevant.

1161 ↔ = No significant effect.

1162 ? = Conflicting data.

1163

1164 **Estrogen-Containing Oral Contraceptives:** In 16 female volunteers, an oral
1165 contraceptive preparation containing 30 mcg ethinylestradiol and 150 mcg levonorgestrel
1166 increased the apparent clearance of lamotrigine (300 mg/day) by approximately 2-fold with mean
1167 decreases in AUC of 52% and in C_{max} of 39%. In this study, trough serum lamotrigine
1168 concentrations gradually increased and were approximately 2-fold higher on average at the end
1169 of the week of the inactive hormone preparation compared with trough lamotrigine
1170 concentrations at the end of the active hormone cycle.

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 44

1171 Gradual transient increases in lamotrigine plasma levels (approximate 2-fold increase)
1172 occurred during the week of inactive hormone preparation (pill-free week) for women not also
1173 taking a drug that increased the clearance of lamotrigine (carbamazepine, phenytoin,
1174 phenobarbital, primidone, or other drugs such as rifampin and the protease inhibitors
1175 lopinavir/ritonavir and atazanavir/ritonavir that induce lamotrigine glucuronidation) [*see Drug*
1176 *Interactions (7)*]. The increase in lamotrigine plasma levels will be greater if the dose of
1177 LAMICTAL is increased in the few days before or during the pill-free week. Increases in
1178 lamotrigine plasma levels could result in dose-dependent adverse reactions.

1179 In the same study, coadministration of lamotrigine (300 mg/day) in 16 female volunteers
1180 did not affect the pharmacokinetics of the ethinylestradiol component of the oral contraceptive
1181 preparation. There were mean decreases in the AUC and C_{max} of the levonorgestrel component of
1182 19% and 12%, respectively. Measurement of serum progesterone indicated that there was no
1183 hormonal evidence of ovulation in any of the 16 volunteers, although measurement of serum
1184 FSH, LH, and estradiol indicated that there was some loss of suppression of the hypothalamic-
1185 pituitary-ovarian axis.

1186 The effects of doses of lamotrigine other than 300 mg/day have not been systematically
1187 evaluated in controlled clinical trials.

1188 The clinical significance of the observed hormonal changes on ovulatory activity is
1189 unknown. However, the possibility of decreased contraceptive efficacy in some patients cannot
1190 be excluded. Therefore, patients should be instructed to promptly report changes in their
1191 menstrual pattern (e.g., break-through bleeding).

1192 Dosage adjustments may be necessary for women receiving estrogen-containing oral
1193 contraceptive preparations [*see Dosage and Administration (2.1)*].

1194 **Other Hormonal Contraceptives or Hormone Replacement Therapy:** The effect of
1195 other hormonal contraceptive preparations or hormone replacement therapy on the
1196 pharmacokinetics of lamotrigine has not been systematically evaluated. It has been reported that
1197 ethinylestradiol, not progestogens, increased the clearance of lamotrigine up to 2-fold, and the
1198 progestin-only pills had no effect on lamotrigine plasma levels. Therefore, adjustments to the
1199 dosage of LAMICTAL in the presence of progestogens alone will likely not be needed.

1200 **Atazanavir/Ritonavir:** In a study in healthy volunteers, daily doses of
1201 atazanavir/ritonavir (300 mg/100 mg) reduced the plasma AUC and C_{max} of lamotrigine (single
1202 100-mg dose) by an average of 32% and 6%, respectively, and shortened the elimination half-
1203 lives by 27%. In the presence of atazanavir/ritonavir (300 mg/100 mg), the metabolite-to-
1204 lamotrigine ratio was increased from 0.45 to 0.71 consistent with induction of glucuronidation.
1205 The pharmacokinetics of atazanavir/ritonavir were similar in the presence of concomitant
1206 lamotrigine to the historical data of the pharmacokinetics in the absence of lamotrigine.

1207 **Bupropion:** The pharmacokinetics of a 100-mg single dose of lamotrigine in healthy
1208 volunteers (n = 12) were not changed by coadministration of bupropion sustained-release
1209 formulation (150 mg twice daily) starting 11 days before lamotrigine.

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 45

1210 Carbamazepine: Lamotrigine has no appreciable effect on steady-state carbamazepine
1211 plasma concentration. Limited clinical data suggest there is a higher incidence of dizziness,
1212 diplopia, ataxia, and blurred vision in patients receiving carbamazepine with lamotrigine than in
1213 patients receiving other AEDs with lamotrigine [see *Adverse Reactions (6.1)*]. The mechanism
1214 of this interaction is unclear. The effect of lamotrigine on plasma concentrations of
1215 carbamazepine-epoxide is unclear. In a small subset of patients (n = 7) studied in a placebo-
1216 controlled trial, lamotrigine had no effect on carbamazepine-epoxide plasma concentrations, but
1217 in a small, uncontrolled study (n = 9), carbamazepine-epoxide levels increased.

1218 The addition of carbamazepine decreases lamotrigine steady-state concentrations by
1219 approximately 40%.

1220 Felbamate: In a trial in 21 healthy volunteers, coadministration of felbamate (1,200 mg
1221 twice daily) with lamotrigine (100 mg twice daily for 10 days) appeared to have no clinically
1222 relevant effects on the pharmacokinetics of lamotrigine.

1223 Folate Inhibitors: Lamotrigine is a weak inhibitor of dihydrofolate reductase. Prescribers
1224 should be aware of this action when prescribing other medications that inhibit folate metabolism.

1225 Gabapentin: Based on a retrospective analysis of plasma levels in 34 subjects who
1226 received lamotrigine both with and without gabapentin, gabapentin does not appear to change the
1227 apparent clearance of lamotrigine.

1228 Levetiracetam: Potential drug interactions between levetiracetam and lamotrigine were
1229 assessed by evaluating serum concentrations of both agents during placebo-controlled clinical
1230 trials. These data indicate that lamotrigine does not influence the pharmacokinetics of
1231 levetiracetam and that levetiracetam does not influence the pharmacokinetics of lamotrigine.

1232 Lithium: The pharmacokinetics of lithium were not altered in healthy subjects (n = 20) by
1233 coadministration of lamotrigine (100 mg/day) for 6 days.

1234 Lopinavir/Ritonavir: The addition of lopinavir (400 mg twice daily)/ritonavir (100 mg
1235 twice daily) decreased the AUC, C_{max} , and elimination half-life of lamotrigine by approximately
1236 50% to 55.4% in 18 healthy subjects. The pharmacokinetics of lopinavir/ritonavir were similar
1237 with concomitant lamotrigine, compared to that in historical controls.

1238 Olanzapine: The AUC and C_{max} of olanzapine were similar following the addition of
1239 olanzapine (15 mg once daily) to lamotrigine (200 mg once daily) in healthy male volunteers
1240 (n = 16) compared with the AUC and C_{max} in healthy male volunteers receiving olanzapine alone
1241 (n = 16).

1242 In the same trial, the AUC and C_{max} of lamotrigine were reduced on average by 24% and
1243 20%, respectively, following the addition of olanzapine to lamotrigine in healthy male volunteers
1244 compared with those receiving lamotrigine alone. This reduction in lamotrigine plasma
1245 concentrations is not expected to be clinically relevant.

1246 Oxcarbazepine: The AUC and C_{max} of oxcarbazepine and its active 10-monohydroxy
1247 oxcarbazepine metabolite were not significantly different following the addition of
1248 oxcarbazepine (600 mg twice daily) to lamotrigine (200 mg once daily) in healthy male

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 46

1249 volunteers (n = 13) compared with healthy male volunteers receiving oxcarbazepine alone
1250 (n = 13).

1251 In the same trial, the AUC and C_{max} of lamotrigine were similar following the addition of
1252 oxcarbazepine (600 mg twice daily) to lamotrigine in healthy male volunteers compared with
1253 those receiving lamotrigine alone. Limited clinical data suggest a higher incidence of headache,
1254 dizziness, nausea, and somnolence with coadministration of lamotrigine and oxcarbazepine
1255 compared with lamotrigine alone or oxcarbazepine alone.

1256 Phenobarbital, Primidone: The addition of phenobarbital or primidone decreases
1257 lamotrigine steady-state concentrations by approximately 40%.

1258 Phenytoin: Lamotrigine has no appreciable effect on steady-state phenytoin plasma
1259 concentrations in patients with epilepsy. The addition of phenytoin decreases lamotrigine steady-
1260 state concentrations by approximately 40%.

1261 Pregabalin: Steady-state trough plasma concentrations of lamotrigine were not affected
1262 by concomitant pregabalin (200 mg 3 times daily) administration. There are no pharmacokinetic
1263 interactions between lamotrigine and pregabalin.

1264 Rifampin: In 10 male volunteers, rifampin (600 mg/day for 5 days) significantly
1265 increased the apparent clearance of a single 25-mg dose of lamotrigine by approximately 2-fold
1266 (AUC decreased by approximately 40%).

1267 Risperidone: In a 14 healthy volunteers study, multiple oral doses of lamotrigine 400 mg
1268 daily had no clinically significant effect on the single-dose pharmacokinetics of risperidone 2 mg
1269 and its active metabolite 9-OH risperidone. Following the coadministration of risperidone 2 mg
1270 with lamotrigine, 12 of the 14 volunteers reported somnolence compared with 1 out of 20 when
1271 risperidone was given alone, and none when lamotrigine was administered alone.

1272 Topiramate: Topiramate resulted in no change in plasma concentrations of lamotrigine.
1273 Administration of lamotrigine resulted in a 15% increase in topiramate concentrations.

1274 Valproate: When lamotrigine was administered to healthy volunteers (n = 18) receiving
1275 valproate, the trough steady-state valproate plasma concentrations decreased by an average of
1276 25% over a 3-week period, and then stabilized. However, adding lamotrigine to the existing
1277 therapy did not cause a change in valproate plasma concentrations in either adult or pediatric
1278 patients in controlled clinical trials.

1279 The addition of valproate increased lamotrigine steady-state concentrations in normal
1280 volunteers by slightly more than 2-fold. In 1 trial, maximal inhibition of lamotrigine clearance
1281 was reached at valproate doses between 250 and 500 mg/day and did not increase as the
1282 valproate dose was further increased.

1283 Zonisamide: In a study in 18 patients with epilepsy, coadministration of zonisamide
1284 (200 to 400 mg/day) with lamotrigine (150 to 500 mg/day for 35 days) had no significant effect
1285 on the pharmacokinetics of lamotrigine.

1286 Known Inducers or Inhibitors of Glucuronidation: Drugs other than those listed above
1287 have not been systematically evaluated in combination with lamotrigine. Since lamotrigine is

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 47

1288 metabolized predominately by glucuronic acid conjugation, drugs that are known to induce or
1289 inhibit glucuronidation may affect the apparent clearance of lamotrigine and doses of lamotrigine
1290 may require adjustment based on clinical response.

1291 Other: Results of in vitro experiments suggest that clearance of lamotrigine is unlikely to
1292 be reduced by concomitant administration of amitriptyline, clonazepam, clozapine, fluoxetine,
1293 haloperidol, lorazepam, phenelzine, sertraline, or trazodone.

1294 Results of in vitro experiments suggest that lamotrigine does not reduce the clearance of
1295 drugs eliminated predominantly by CYP2D6.

1296 Specific Populations: Subjects With Renal Impairment: Twelve volunteers with
1297 chronic renal failure (mean creatinine clearance: 13 mL/min, range: 6 to 23) and another 6
1298 individuals undergoing hemodialysis were each given a single 100-mg dose of lamotrigine. The
1299 mean plasma half-lives determined in the study were 42.9 hours (chronic renal failure),
1300 13.0 hours (during hemodialysis), and 57.4 hours (between hemodialysis) compared with
1301 26.2 hours in healthy volunteers. On average, approximately 20% (range: 5.6 to 35.1) of the
1302 amount of lamotrigine present in the body was eliminated by hemodialysis during a 4-hour
1303 session [*see Dosage and Administration (2.1)*].

1304 Hepatic Disease: The pharmacokinetics of lamotrigine following a single 100-mg
1305 dose of lamotrigine were evaluated in 24 subjects with mild, moderate, and severe hepatic
1306 impairment (Child-Pugh Classification system) and compared with 12 subjects without hepatic
1307 impairment. The subjects with severe hepatic impairment were without ascites (n = 2) or with
1308 ascites (n = 5). The mean apparent clearances of lamotrigine in subjects with mild (n = 12),
1309 moderate (n = 5), severe without ascites (n = 2), and severe with ascites (n = 5) liver impairment
1310 were 0.30 ± 0.09 , 0.24 ± 0.1 , 0.21 ± 0.04 , and 0.15 ± 0.09 mL/min/kg, respectively, as compared
1311 with 0.37 ± 0.1 mL/min/kg in the healthy controls. Mean half-lives of lamotrigine in subjects
1312 with mild, moderate, severe without ascites, and severe with ascites hepatic impairment were
1313 46 ± 20 , 72 ± 44 , 67 ± 11 , and 100 ± 48 hours, respectively, as compared with 33 ± 7 hours in
1314 healthy controls [*see Dosage and Administration (2.1)*].

1315 Age: Pediatric Subjects: The pharmacokinetics of lamotrigine following a single
1316 2-mg/kg dose were evaluated in 2 studies in pediatric subjects (n = 29 for subjects aged 10
1317 months to 5.9 years and n = 26 for subjects aged 5 to 11 years). Forty-three subjects received
1318 concomitant therapy with other AEDs and 12 subjects received lamotrigine as monotherapy.
1319 Lamotrigine pharmacokinetic parameters for pediatric patients are summarized in Table 16.

1320 Population pharmacokinetic analyses involving subjects aged 2 to 18 years demonstrated
1321 that lamotrigine clearance was influenced predominantly by total body weight and concurrent
1322 AED therapy. The oral clearance of lamotrigine was higher, on a body weight basis, in pediatric
1323 patients than in adults. Weight-normalized lamotrigine clearance was higher in those subjects
1324 weighing less than 30 kg compared with those weighing greater than 30 kg. Accordingly,
1325 patients weighing less than 30 kg may need an increase of as much as 50% in maintenance doses,
1326 based on clinical response, as compared with subjects weighing more than 30 kg being

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 48

1327 administered the same AEDs [see *Dosage and Administration (2.2)*]. These analyses also
1328 revealed that, after accounting for body weight, lamotrigine clearance was not significantly
1329 influenced by age. Thus, the same weight-adjusted doses should be administered to children
1330 irrespective of differences in age. Concomitant AEDs which influence lamotrigine clearance in
1331 adults were found to have similar effects in children.

1332

1333

Table 16. Mean Pharmacokinetic Parameters in Pediatric Subjects With Epilepsy

Pediatric Study Population	Number of Subjects	T_{max} (h)	t_{1/2} (h)	CL/F (mL/min/kg)
Ages 10 months-5.3 years				
Subjects taking carbamazepine, phenytoin, phenobarbital, or primidone ^a	10	3.0 (1.0-5.9)	7.7 (5.7-11.4)	3.62 (2.44-5.28)
Subjects 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)
Subjects taking valproate only	8	2.9 (1.0-6.0)	44.9 (29.5-52.5)	0.47 (0.23-0.77)
Ages 5-11 years				
Subjects taking carbamazepine, phenytoin, phenobarbital, or primidone ^a	7	1.6 (1.0-3.0)	7.0 (3.8-9.8)	2.54 (1.35-5.58)
Subjects taking carbamazepine, phenytoin, phenobarbital, or primidone ^a plus valproate	8	3.3 (1.0-6.4)	19.1 (7.0-31.2)	0.89 (0.39-1.93)
Subjects taking valproate only ^b	3	4.5 (3.0-6.0)	65.8 (50.7-73.7)	0.24 (0.21-0.26)
Ages 13-18 years				
Subjects taking carbamazepine, phenytoin, phenobarbital, or primidone ^a	11	— ^c	— ^c	1.3
Subjects taking carbamazepine, phenytoin, phenobarbital, or primidone ^a plus valproate	8	— ^c	— ^c	0.5
Subjects taking valproate only	4	— ^c	— ^c	0.3

1334

1335

1336

1337

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

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 49

1338 ^b Two subjects were included in the calculation for mean T_{\max} .

1339 ^c Parameter not estimated.

1340

1341 *Elderly:* The pharmacokinetics of lamotrigine following a single 150-mg dose of
1342 lamotrigine were evaluated in 12 elderly volunteers between the ages of 65 and 76 years (mean
1343 creatinine clearance = 61 mL/min, range: 33 to 108 mL/min). The mean half-life of lamotrigine
1344 in these subjects was 31.2 hours (range: 24.5 to 43.4 hours), and the mean clearance was
1345 0.40 mL/min/kg (range: 0.26 to 0.48 mL/min/kg).

1346 *Gender:* The clearance of lamotrigine is not affected by gender. However, during
1347 dose escalation of lamotrigine in 1 clinical trial in patients with epilepsy on a stable dose of
1348 valproate (n = 77), mean trough lamotrigine concentrations unadjusted for weight were 24% to
1349 45% higher (0.3 to 1.7 mcg/mL) in females than in males.

1350 *Race:* The apparent oral clearance of lamotrigine was 25% lower in non-Caucasians
1351 than Caucasians.

1352 **13 NONCLINICAL TOXICOLOGY**

1353 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

1354 No evidence of carcinogenicity was seen in 1 mouse study or 2 rat studies following oral
1355 administration of lamotrigine for up to 2 years at maximum tolerated doses (30 mg/kg/day for
1356 mice and 10 to 15 mg/kg/day for rats, doses that are equivalent to 90 mg/m² and 60 to 90 mg/m²,
1357 respectively). Steady-state plasma concentrations ranged from 1 to 4 mcg/mL in the mouse study
1358 and 1 to 10 mcg/mL in the rat study. Plasma concentrations associated with the recommended
1359 human doses of 300 to 500 mg/day are generally in the range of 2 to 5 mcg/mL, but
1360 concentrations as high as 19 mcg/mL have been recorded.

1361 Lamotrigine was not mutagenic in the presence or absence of metabolic activation when
1362 tested in 2 gene mutation assays (the Ames test and the in vitro mammalian mouse lymphoma
1363 assay). In 2 cytogenetic assays (the in vitro human lymphocyte assay and the in vivo rat bone
1364 marrow assay), lamotrigine did not increase the incidence of structural or numerical
1365 chromosomal abnormalities.

1366 No evidence of impairment of fertility was detected in rats given oral doses of
1367 lamotrigine up to 2.4 times the highest usual human maintenance dose of 8.33 mg/kg/day or
1368 0.4 times the human dose on a mg/m² basis. The effect of lamotrigine on human fertility is
1369 unknown.

1370 **14 CLINICAL STUDIES**

1371 **14.1 Epilepsy**

1372 Monotherapy With LAMICTAL in Adults With Partial-Onset Seizures Already
1373 Receiving Treatment With Carbamazepine, Phenytoin, Phenobarbital, or Primidone as
1374 the Single Antiepileptic Drug: The effectiveness of monotherapy with LAMICTAL was
1375 established in a multicenter, double-blind clinical trial enrolling 156 adult outpatients with

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 50

1376 partial-onset seizures. The patients experienced at least 4 simple partial-onset, complex partial-
1377 onset, and/or secondarily generalized seizures during each of 2 consecutive 4-week periods while
1378 receiving carbamazepine or phenytoin monotherapy during baseline. LAMICTAL (target dose of
1379 500 mg/day) or valproate (1,000 mg/day) was added to either carbamazepine or phenytoin
1380 monotherapy over a 4-week period. Patients were then converted to monotherapy with
1381 LAMICTAL or valproate during the next 4 weeks, then continued on monotherapy for an
1382 additional 12-week period.

1383 Trial endpoints were completion of all weeks of trial treatment or meeting an escape
1384 criterion. Criteria for escape relative to baseline were: (1) doubling of average monthly seizure
1385 count, (2) doubling of highest consecutive 2-day seizure frequency, (3) emergence of a new
1386 seizure type (defined as a seizure that did not occur during the 8-week baseline) that is more
1387 severe than seizure types that occur during study treatment, or (4) clinically significant
1388 prolongation of generalized tonic-clonic seizures. The primary efficacy variable was the
1389 proportion of patients in each treatment group who met escape criteria.

1390 The percentages of patients who met escape criteria were 42% (32/76) in the group
1391 receiving LAMICTAL and 69% (55/80) in the valproate group. The difference in the percentage
1392 of patients meeting escape criteria was statistically significant ($P = 0.0012$) in favor of
1393 LAMICTAL. No differences in efficacy based on age, sex, or race were detected.

1394 Patients in the control group were intentionally treated with a relatively low dose of
1395 valproate; as such, the sole objective of this trial was to demonstrate the effectiveness and safety
1396 of monotherapy with LAMICTAL, and cannot be interpreted to imply the superiority of
1397 LAMICTAL to an adequate dose of valproate.

1398 Adjunctive Therapy With LAMICTAL in Adults With Partial-Onset Seizures: The
1399 effectiveness of LAMICTAL as adjunctive therapy (added to other AEDs) was initially
1400 established in 3 pivotal, multicenter, placebo-controlled, double-blind clinical trials in 355 adults
1401 with refractory partial-onset seizures. The patients had a history of at least 4 partial-onset
1402 seizures per month in spite of receiving 1 or more AEDs at therapeutic concentrations and in 2 of
1403 the trials were observed on their established AED regimen during baselines that varied between 8
1404 to 12 weeks. In the third trial, patients were not observed in a prospective baseline. In patients
1405 continuing to have at least 4 seizures per month during the baseline, LAMICTAL or placebo was
1406 then added to the existing therapy. In all 3 trials, change from baseline in seizure frequency was
1407 the primary measure of effectiveness. The results given below are for all partial-onset seizures in
1408 the intent-to-treat population (all patients who received at least 1 dose of treatment) in each trial,
1409 unless otherwise indicated. The median seizure frequency at baseline was 3 per week while the
1410 mean at baseline was 6.6 per week for all patients enrolled in efficacy trials.

1411 One trial ($n = 216$) was a double-blind, placebo-controlled, parallel trial consisting of a
1412 24-week treatment period. Patients could not be on more than 2 other anticonvulsants and
1413 valproate was not allowed. Patients were randomized to receive placebo, a target dose of
1414 300 mg/day of LAMICTAL, or a target dose of 500 mg/day of LAMICTAL. The median

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 51

1415 reductions in the frequency of all partial-onset seizures relative to baseline were 8% in patients
1416 receiving placebo, 20% in patients receiving 300 mg/day of LAMICTAL, and 36% in patients
1417 receiving 500 mg/day of LAMICTAL. The seizure frequency reduction was statistically
1418 significant in the 500-mg/day group compared with the placebo group, but not in the 300-mg/day
1419 group.

1420 A second trial (n = 98) was a double-blind, placebo-controlled, randomized, crossover
1421 trial consisting of two 14-week treatment periods (the last 2 weeks of which consisted of dose
1422 tapering) separated by a 4-week washout period. Patients could not be on more than 2 other
1423 anticonvulsants and valproate was not allowed. The target dose of LAMICTAL was 400 mg/day.
1424 When the first 12 weeks of the treatment periods were analyzed, the median change in seizure
1425 frequency was a 25% reduction on LAMICTAL compared with placebo ($P < 0.001$).

1426 The third trial (n = 41) was a double-blind, placebo-controlled, crossover trial consisting
1427 of two 12-week treatment periods separated by a 4-week washout period. Patients could not be
1428 on more than 2 other anticonvulsants. Thirteen patients were on concomitant valproate; these
1429 patients received 150 mg/day of LAMICTAL. The 28 other patients had a target dose of
1430 300 mg/day of LAMICTAL. The median change in seizure frequency was a 26% reduction on
1431 LAMICTAL compared with placebo ($P < 0.01$).

1432 No differences in efficacy based on age, sex, or race, as measured by change in seizure
1433 frequency, were detected.

1434 Adjunctive Therapy With LAMICTAL in Pediatric Patients With Partial-Onset
1435 Seizures: The effectiveness of LAMICTAL as adjunctive therapy in pediatric patients with
1436 partial-onset seizures was established in a multicenter, double-blind, placebo-controlled trial in
1437 199 patients aged 2 to 16 years (n = 98 on LAMICTAL, n = 101 on placebo). Following an 8-
1438 week baseline phase, patients were randomized to 18 weeks of treatment with LAMICTAL or
1439 placebo added to their current AED regimen of up to 2 drugs. Patients were dosed based on body
1440 weight and valproate use. Target doses were designed to approximate 5 mg/kg/day for patients
1441 taking valproate (maximum dose: 250 mg/day) and 15 mg/kg/day for the patients not taking
1442 valproate (maximum dose: 750 mg/day). The primary efficacy endpoint was percentage change
1443 from baseline in all partial-onset seizures. For the intent-to-treat population, the median
1444 reduction of all partial-onset seizures was 36% in patients treated with LAMICTAL and 7% on
1445 placebo, a difference that was statistically significant ($P < 0.01$).

1446 Adjunctive Therapy With LAMICTAL in Pediatric and Adult Patients With Lennox-
1447 Gastaut Syndrome: The effectiveness of LAMICTAL as adjunctive therapy in patients with
1448 Lennox-Gastaut syndrome was established in a multicenter, double-blind, placebo-controlled
1449 trial in 169 patients aged 3 to 25 years (n = 79 on LAMICTAL, n = 90 on placebo). Following a
1450 4-week, single-blind, placebo phase, patients were randomized to 16 weeks of treatment with
1451 LAMICTAL or placebo added to their current AED regimen of up to 3 drugs. Patients were
1452 dosed on a fixed-dose regimen based on body weight and valproate use. Target doses were
1453 designed to approximate 5 mg/kg/day for patients taking valproate (maximum dose: 200 mg/day)

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 52

1454 and 15 mg/kg/day for patients not taking valproate (maximum dose: 400 mg/day). The primary
1455 efficacy endpoint was percentage change from baseline in major motor seizures (atonic, tonic,
1456 major myoclonic, and tonic-clonic seizures). For the intent-to-treat population, the median
1457 reduction of major motor seizures was 32% in patients treated with LAMICTAL and 9% on
1458 placebo, a difference that was statistically significant ($P < 0.05$). Drop attacks were significantly
1459 reduced by LAMICTAL (34%) compared with placebo (9%), as were tonic-clonic seizures (36%
1460 reduction versus 10% increase for LAMICTAL and placebo, respectively).

1461 Adjunctive Therapy With LAMICTAL in Pediatric and Adult Patients With Primary
1462 Generalized Tonic-Clonic Seizures: The effectiveness of LAMICTAL as adjunctive therapy
1463 in patients with PGTC seizures was established in a multicenter, double-blind, placebo-
1464 controlled trial in 117 pediatric and adult patients aged 2 years and older ($n = 58$ on
1465 LAMICTAL, $n = 59$ on placebo). Patients with at least 3 PGTC seizures during an 8-week
1466 baseline phase were randomized to 19 to 24 weeks of treatment with LAMICTAL or placebo
1467 added to their current AED regimen of up to 2 drugs. Patients were dosed on a fixed-dose
1468 regimen, with target doses ranging from 3 to 12 mg/kg/day for pediatric patients and from 200 to
1469 400 mg/day for adult patients based on concomitant AEDs.

1470 The primary efficacy endpoint was percentage change from baseline in PGTC seizures.
1471 For the intent-to-treat population, the median percent reduction in PGTC seizures was 66% in
1472 patients treated with LAMICTAL and 34% on placebo, a difference that was statistically
1473 significant ($P = 0.006$).

1474 **14.2 Bipolar Disorder**

1475 The effectiveness of LAMICTAL in the maintenance treatment of bipolar I disorder was
1476 established in 2 multicenter, double-blind, placebo-controlled trials in adult patients who met
1477 DSM-IV criteria for bipolar I disorder. Trial 1 enrolled patients with a current or recent (within
1478 60 days) depressive episode as defined by DSM-IV and Trial 2 included patients with a current
1479 or recent (within 60 days) episode of mania or hypomania as defined by DSM-IV. Both trials
1480 included a cohort of patients (30% of 404 subjects in Trial 1 and 28% of 171 patients in Trial 2)
1481 with rapid cycling bipolar disorder (4 to 6 episodes per year).

1482 In both trials, patients were titrated to a target dose of 200 mg of LAMICTAL as add-on
1483 therapy or as monotherapy with gradual withdrawal of any psychotropic medications during an
1484 8- to 16-week open-label period. Overall 81% of 1,305 patients participating in the open-label
1485 period were receiving 1 or more other psychotropic medications, including benzodiazepines,
1486 selective serotonin reuptake inhibitors (SSRIs), atypical antipsychotics (including olanzapine),
1487 valproate, or lithium, during titration of LAMICTAL. Patients with a CGI-severity score of 3 or
1488 less maintained for at least 4 continuous weeks, including at least the final week on monotherapy
1489 with LAMICTAL, were randomized to a placebo-controlled, double-blind treatment period for
1490 up to 18 months. The primary endpoint was TIME (time to intervention for a mood episode or
1491 one that was emerging, time to discontinuation for either an adverse event that was judged to be

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 53

1492 related to bipolar disorder, or for lack of efficacy). The mood episode could be depression,
1493 mania, hypomania, or a mixed episode.

1494 In Trial 1, patients received double-blind monotherapy with LAMICTAL 50 mg/day (n =
1495 50), LAMICTAL 200 mg/day (n = 124), LAMICTAL 400 mg/day (n = 47), or placebo
1496 (n = 121). LAMICTAL (200- and 400-mg/day treatment groups combined) was superior to
1497 placebo in delaying the time to occurrence of a mood episode. Separate analyses of the 200- and
1498 400-mg/day dose groups revealed no added benefit from the higher dose.

1499 In Trial 2, patients received double-blind monotherapy with LAMICTAL (100 to
1500 400 mg/day, n = 59), or placebo (n = 70). LAMICTAL was superior to placebo in delaying time
1501 to occurrence of a mood episode. The mean dose of LAMICTAL was about 211 mg/day.

1502 Although these trials were not designed to separately evaluate time to the occurrence of
1503 depression or mania, a combined analysis for the 2 trials revealed a statistically significant
1504 benefit for LAMICTAL over placebo in delaying the time to occurrence of both depression and
1505 mania, although the finding was more robust for depression.

1506 **16 HOW SUPPLIED/STORAGE AND HANDLING**

1507 **LAMICTAL (lamotrigine) Tablets**

1508 25 mg, white, scored, shield-shaped tablets debossed with “LAMICTAL” and “25”,
1509 bottles of 100 (NDC 0173-0633-02).

1510 Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP
1511 Controlled Room Temperature] in a dry place.

1512 100 mg, peach, scored, shield-shaped tablets debossed with “LAMICTAL” and “100”,
1513 bottles of 100 (NDC 0173-0642-55).

1514 150 mg, cream, scored, shield-shaped tablets debossed with “LAMICTAL” and “150”,
1515 bottles of 60 (NDC 0173-0643-60).

1516 200 mg, blue, scored, shield-shaped tablets debossed with “LAMICTAL” and “200”,
1517 bottles of 60 (NDC 0173-0644-60).

1518 Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP
1519 Controlled Room Temperature] in a dry place and protect from light.

1520

1521 **LAMICTAL (lamotrigine) Starter Kit for Patients Taking Valproate (Blue Kit)**

1522 25 mg, white, scored, shield-shaped tablets debossed with “LAMICTAL” and “25”,
1523 blisterpack of 35 tablets (NDC 0173-0633-10).

1524 Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP
1525 Controlled Room Temperature] in a dry place.

1526 **LAMICTAL (lamotrigine) Starter Kit for Patients Taking Carbamazepine, 1527 Phenytoin, Phenobarbital, or Primidone and Not Taking Valproate (Green Kit)**

1528 25 mg, white, scored, shield-shaped tablets debossed with “LAMICTAL” and “25” and
1529 100 mg, peach, scored, shield-shaped tablets debossed with “LAMICTAL” and “100”,
1530 blisterpack of 98 tablets (84/25-mg tablets and 14/100-mg tablets) (NDC 0173-0817-28).

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 54

1531 Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP
1532 Controlled Room Temperature] in a dry place and protect from light.

1533 **LAMICTAL (lamotrigine) Starter Kit for Patients Not Taking Carbamazepine,**
1534 **Phenytoin, Phenobarbital, Primidone, or Valproate (Orange Kit)**

1535 25 mg, white, scored, shield-shaped tablets debossed with “LAMICTAL” and “25” and
1536 100 mg, peach, scored, shield-shaped tablets debossed with “LAMICTAL” and “100”,
1537 blisterpack of 49 tablets (42/25-mg tablets and 7/100-mg tablets) (NDC 0173-0594-02).

1538 Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP
1539 Controlled Room Temperature] in a dry place and protect from light.

1540

1541 **LAMICTAL (lamotrigine) Chewable Dispersible Tablets**

1542 2 mg, white to off-white, round tablets debossed with “LTG” over “2”, bottles of 30
1543 (NDC 0173-0699-00). ORDER DIRECTLY FROM GlaxoSmithKline 1-800-334-4153.

1544 5 mg, white to off-white, caplet-shaped tablets debossed with “GX CL2”, bottles of 100
1545 (NDC 0173-0526-00).

1546 25 mg, white, super elliptical-shaped tablets debossed with “GX CL5”, bottles of 100
1547 (NDC 0173-0527-00).

1548 Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP
1549 Controlled Room Temperature] in a dry place.

1550

1551 **LAMICTAL ODT (lamotrigine) Orally Disintegrating Tablets**

1552 25 mg, white to off-white, round, flat-faced, radius-edged tablets debossed with “LMT”
1553 on one side and “25” on the other, Maintenance Packs of 30 (NDC 0173-0772-02).

1554 50 mg, white to off-white, round, flat-faced, radius-edged tablets debossed with “LMT”
1555 on one side and “50” on the other, Maintenance Packs of 30 (NDC 0173-0774-02).

1556 100 mg, white to off-white, round, flat-faced, radius-edged tablets debossed with
1557 “LAMICTAL” on one side and “100” on the other, Maintenance Packs of 30 (NDC 0173-0776-
1558 02).

1559 200 mg, white to off-white, round, flat-faced, radius-edged tablets debossed with
1560 “LAMICTAL” on one side and “200” on the other, Maintenance Packs of 30 (NDC 0173-0777-
1561 02).

1562 Store between 20°C and 25°C (68°F and 77°F); with excursions permitted between 15°C
1563 and 30°C (59°F and 86°F).

1564 **LAMICTAL ODT (lamotrigine) Patient Titration Kit for Patients Taking Valproate**
1565 **(Blue ODT Kit)**

1566 25 mg, white to off-white, round, flat-faced, radius-edged tablets debossed with “LMT”
1567 on one side and “25” on the other, and 50 mg, white to off-white, round, flat-faced, radius-edged
1568 tablets debossed with “LMT” on one side and “50” on the other, blisterpack of 28 tablets
1569 (21/25-mg tablets and 7/50-mg tablets) (NDC 0173-0779-00).

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 55

1570 **LAMICTAL ODT (lamotrigine) Patient Titration Kit for Patients Taking**
1571 **Carbamazepine, Phenytoin, Phenobarbital, or Primidone and Not Taking Valproate**
1572 **(Green ODT Kit)**

1573 50 mg, white to off-white, round, flat-faced, radius-edged tablets debossed with “LMT”
1574 on one side and “50” on the other, and 100 mg, white to off-white, round, flat-faced, radius-
1575 edged tablets debossed with “LAMICTAL” on one side and “100” on the other, blisterpack of 56
1576 tablets (42/50-mg tablets and 14/100-mg tablets) (NDC 0173-0780-00).

1577 **LAMICTAL ODT (lamotrigine) Patient Titration Kit for Patients Not Taking**
1578 **Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate (Orange ODT Kit)**

1579 25 mg, white to off-white, round, flat-faced, radius-edged tablets debossed with “LMT”
1580 on one side and “25” on the other, 50 mg, white to off-white, round, flat-faced, radius-edged
1581 tablets debossed with “LMT” on one side and “50” on the other, and 100 mg, white to off-white,
1582 round, flat-faced, radius-edged tablets debossed with “LAMICTAL” on one side and “100” on
1583 the other, blisterpack of 35 (14/25-mg tablets, 14/50-mg tablets, and 7/100-mg tablets) (NDC
1584 0173-0778-00).

1585 Store between 20°C and 25°C (68°F and 77°F); with excursions permitted between 15°C
1586 and 30°C (59°F and 86°F).

1587 **Blisterpacks:** If the product is dispensed in a blisterpack, the patient should be advised to
1588 examine the blisterpack before use and not use if blisters are torn, broken, or missing.

1589 **17 PATIENT COUNSELING INFORMATION**

1590 Advise the patient to read the FDA-approved patient labeling (Medication Guide).

1591 **Rash:** Prior to initiation of treatment with LAMICTAL, inform patients that a rash or
1592 other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy) may herald a serious
1593 medical event and instruct them to report any such occurrence to their physician immediately.

1594 **Multiorgan Hypersensitivity Reactions, Blood Dyscrasias, and Organ Failure:**
1595 Inform patients that multiorgan hypersensitivity reactions and acute multiorgan failure may
1596 occur with LAMICTAL. Isolated organ failure or isolated blood dyscrasias without evidence of
1597 multiorgan hypersensitivity may also occur. Instruct patients to contact their physician
1598 immediately if they experience any signs or symptoms of these conditions [*see Warnings and*
1599 *Precautions (5.2, 5.3)].*

1600 **Suicidal Thinking and Behavior:** Inform patients, their caregivers, and families that
1601 AEDs, including LAMICTAL, may increase the risk of suicidal thoughts and behavior. Instruct
1602 them to be alert for the emergence or worsening of symptoms of depression, any unusual
1603 changes in mood or behavior, or the emergence of suicidal thoughts or behavior or thoughts
1604 about self-harm. They should immediately report behaviors of concern to their physician.

1605 **Worsening of Seizures:** Advise patients to notify their physician if worsening of
1606 seizure control occurs.

1607 **Central Nervous System Adverse Effects:** Inform patients that LAMICTAL may
1608 cause dizziness, somnolence, and other symptoms and signs of central nervous system

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 56

1609 depression. Accordingly, instruct them neither to drive a car nor to operate other complex
1610 machinery until they have gained sufficient experience on LAMICTAL to gauge whether or not
1611 it adversely affects their mental and/or motor performance.

1612 Pregnancy and Nursing: Instruct patients to notify their physician if they become
1613 pregnant or intend to become pregnant during therapy and if they intend to breastfeed or are
1614 breastfeeding an infant.

1615 Encourage patients to enroll in the NAAED Pregnancy Registry if they become pregnant.
1616 This registry is collecting information about the safety of antiepileptic drugs during pregnancy.
1617 To enroll, patients can call the toll-free number 1-888-233-2334 [see *Use in Specific Populations*
1618 (8.1)].

1619 Inform patients who intend to breastfeed that LAMICTAL is present in breast milk and
1620 advise them to monitor their child for potential adverse effects of this drug. Discuss the benefits
1621 and risks of continuing breastfeeding.

1622 Oral Contraceptive Use: Instruct women to notify their physician if they plan to start or
1623 stop use of oral contraceptives or other female hormonal preparations. Starting estrogen-
1624 containing oral contraceptives may significantly decrease lamotrigine plasma levels and stopping
1625 estrogen-containing oral contraceptives (including the pill-free week) may significantly increase
1626 lamotrigine plasma levels [see *Warnings and Precautions (5.8), Clinical Pharmacology (12.3)*].
1627 Also instruct women to promptly notify their physician if they experience adverse reactions or
1628 changes in menstrual pattern (e.g., break-through bleeding) while receiving LAMICTAL in
1629 combination with these medications.

1630 Discontinuing LAMICTAL: Instruct patients to notify their physician if they stop taking
1631 LAMICTAL for any reason and not to resume LAMICTAL without consulting their physician.

1632 Aseptic Meningitis: Inform patients that LAMICTAL may cause aseptic meningitis.
1633 Instruct them to notify their physician immediately if they develop signs and symptoms of
1634 meningitis such as headache, fever, nausea, vomiting, stiff neck, rash, abnormal sensitivity to
1635 light, myalgia, chills, confusion, or drowsiness while taking LAMICTAL.

1636 Potential Medication Errors: Medication errors involving LAMICTAL have occurred.
1637 In particular the names LAMICTAL or lamotrigine can be confused with the names of other
1638 commonly used medications. Medication errors may also occur between the different
1639 formulations of LAMICTAL. To reduce the potential of medication errors, write and say
1640 LAMICTAL clearly. Depictions of the LAMICTAL Tablets, Chewable Dispersible Tablets, and
1641 Orally Disintegrating Tablets can be found in the Medication Guide that accompanies the
1642 product to highlight the distinctive markings, colors, and shapes that serve to identify the
1643 different presentations of the drug and thus may help reduce the risk of medication errors. **To**
1644 **avoid a medication error of using the wrong drug or formulation, strongly advise patients**
1645 **to visually inspect their tablets to verify that they are LAMICTAL, as well as the correct**
1646 **formulation of LAMICTAL, each time they fill their prescription** [see *Dosage Forms and*
1647 *Strengths (3.1, 3.2, 3.3), How Supplied/Storage and Handling (16)*].

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 57

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1651 GSK group of companies. The makers of these brands are not affiliated with and do not endorse
1652 the GSK group of companies or its products.

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1662 LMT:xPI

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MEDICATION GUIDE

1665

1666 **LAMICTAL[®] (la-MIK-tal) (lamotrigine) Tablets and Chewable Dispersible**
1667 **Tablets**

1668

LAMICTAL ODT[®] (lamotrigine) Orally Disintegrating Tablets

1669

1670 Read this Medication Guide before you start taking LAMICTAL and each time you
1671 get a refill. There may be new information. This information does not take the place
1672 of talking with your healthcare provider about your medical condition or treatment.
1673 If you have questions about LAMICTAL, ask your healthcare provider or pharmacist.

1674

1675 **What is the most important information I should know about LAMICTAL?**

1676 **1. LAMICTAL may cause a serious skin rash that may cause you to be**
1677 **hospitalized or even cause death.**

1678

1679 There is no way to tell if a mild rash will become more serious. A serious skin
1680 rash can happen at any time during your treatment with LAMICTAL, but is more
1681 likely to happen within the first 2 to 8 weeks of treatment. Children aged
1682 between 2 and 16 years have a higher chance of getting this serious skin rash
while taking LAMICTAL.

1683

The risk of getting a serious skin rash is higher if you:

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 58

- 1684 • take LAMICTAL while taking valproate [DEPAKENE[®] (valproic acid) or
1685 DEPAKOTE[®] (divalproex sodium)].
1686 • take a higher starting dose of LAMICTAL than your healthcare provider
1687 prescribed.
1688 • increase your dose of LAMICTAL faster than prescribed.

1689 **Call your healthcare provider right away if you have any of the**
1690 **following:**

- 1691 • **a skin rash**
1692 • **blistering or peeling of your skin**
1693 • **hives**
1694 • **painful sores in your mouth or around your eyes**

1695 These symptoms may be the first signs of a serious skin reaction. A healthcare
1696 provider should examine you to decide if you should continue taking LAMICTAL.

1697 **2. Other serious reactions, including serious blood problems or liver**
1698 **problems.** LAMICTAL can also cause other types of allergic reactions or serious
1699 problems that may affect organs and other parts of your body like your liver or
1700 blood cells. You may or may not have a rash with these types of reactions. Call
1701 your healthcare provider right away if you have any of these symptoms:

- 1702 • fever
1703 • frequent infections
1704 • severe muscle pain
1705 • swelling of your face, eyes, lips, or tongue
1706 • swollen lymph glands
1707 • unusual bruising or bleeding
1708 • weakness, fatigue
1709 • yellowing of your skin or the white part of your eyes

1710 **3. Like other antiepileptic drugs, LAMICTAL may cause suicidal thoughts or**
1711 **actions in a very small number of people, about 1 in 500.**

1712 **Call a healthcare provider right away if you have any of these**
1713 **symptoms, especially if they are new, worse, or worry you:**

- 1714 • thoughts about suicide or dying
1715 • attempt to commit suicide
1716 • new or worse depression
1717 • new or worse anxiety
1718 • feeling agitated or restless
1719 • panic attacks
1720 • trouble sleeping (insomnia)

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 59

- 1721 • new or worse irritability
- 1722 • acting aggressive, being angry, or violent
- 1723 • acting on dangerous impulses
- 1724 • an extreme increase in activity and talking (mania)
- 1725 • other unusual changes in behavior or mood
- 1726 **Do not stop LAMICTAL without first talking to a healthcare provider.**
- 1727 • Stopping LAMICTAL suddenly can cause serious problems.
- 1728 • Suicidal thoughts or actions can be caused by things other than medicines. If
- 1729 you have suicidal thoughts or actions, your healthcare provider may check
- 1730 for other causes.
- 1731 **How can I watch for early symptoms of suicidal thoughts and actions?**
- 1732 • Pay attention to any changes, especially sudden changes, in mood,
- 1733 behaviors, thoughts, or feelings.
- 1734 • Keep all follow-up visits with your healthcare provider as scheduled.
- 1735 • Call your healthcare provider between visits as needed, especially if you are
- 1736 worried about symptoms.
- 1737 **4. LAMICTAL may rarely cause aseptic meningitis, a serious inflammation**
- 1738 **of the protective membrane that covers the brain and spinal cord.**
- 1739 **Call your healthcare provider right away if you have any of the following**
- 1740 **symptoms:**
- 1741 • headache
- 1742 • fever
- 1743 • nausea
- 1744 • vomiting
- 1745 • stiff neck
- 1746 • rash
- 1747 • unusual sensitivity to light
- 1748 • muscle pains
- 1749 • chills
- 1750 • confusion
- 1751 • drowsiness
- 1752 Meningitis has many causes other than LAMICTAL, which your doctor would
- 1753 check for if you developed meningitis while taking LAMICTAL.
- 1754 **LAMICTAL can have other serious side effects.** For more information ask
- 1755 your healthcare provider or pharmacist. Tell your healthcare provider if you have
- 1756 any side effect that bothers you. Be sure to read the section below entitled
- 1757 “**What are the possible side effects of LAMICTAL?**”

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 60


1758 **5. Patients prescribed LAMICTAL have sometimes been given the wrong**
1759 **medicine because many medicines have names similar to LAMICTAL, so**
1760 **always check that you receive LAMICTAL.**

1761 Taking the wrong medication can cause serious health problems. When your
1762 healthcare provider gives you a prescription for LAMICTAL:




- 1763
- 1764 • Make sure you can read it clearly.
 - 1765 • Talk to your pharmacist to check that you are given the correct medicine.
 - 1766 • Each time you fill your prescription, check the tablets you receive against the pictures of the tablets below.

1767 These pictures show the distinct wording, colors, and shapes of the tablets
1768 that help to identify the right strength of LAMICTAL Tablets, Chewable
1769 Dispersible Tablets, and Orally Disintegrating Tablets. Immediately call your
1770 pharmacist if you receive a LAMICTAL tablet that does not look like one of the
1771 tablets shown below, as you may have received the wrong medication.

1772 **LAMICTAL (lamotrigine) Tablets**

 25 mg, white Imprinted with LAMICTAL 25	 100 mg, peach Imprinted with LAMICTAL 100	 150 mg, cream Imprinted with LAMICTAL 150	 200 mg, blue Imprinted with LAMICTAL 200
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1773 **LAMICTAL (lamotrigine) Chewable Dispersible**
1774 **Tablets**

 2 mg, white Imprinted with LTG 2	 5 mg, white Imprinted with GX CL2	 25 mg, white Imprinted with GX CL5
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NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 61

1775

LAMICTAL ODT (lamotrigine) Orally Disintegrating Tablets

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

1776

1777 **What is LAMICTAL?**

1778 LAMICTAL is a prescription medicine used:

- 1779 1. together with other medicines to treat certain types of seizures (partial-onset
1780 seizures, primary generalized tonic-clonic seizures, generalized seizures of
1781 Lennox-Gastaut syndrome) in people aged 2 years and older.
- 1782 2. alone when changing from 1 other medicine used to treat partial-onset seizures
1783 in people aged 16 years and older.
- 1784 3. for the long-term treatment of bipolar I disorder to lengthen the time between
1785 mood episodes in people aged 18 years and older who have been treated for
1786 mood episodes with other medicine.

1787 It is not known if LAMICTAL is safe or effective in children or teenagers younger
1788 than 18 years with mood disorders such as bipolar disorder or depression.

1789 It is not known if LAMICTAL is safe or effective when used alone as the first
1790 treatment of seizures.

1791

1792 **Who should not take LAMICTAL?**

1793 You should not take LAMICTAL if you have had an allergic reaction to lamotrigine or
1794 to any of the inactive ingredients in LAMICTAL. See the end of this leaflet for a
1795 complete list of ingredients in LAMICTAL.

1796

1797 **What should I tell my healthcare provider before taking LAMICTAL?**

1798 Before taking LAMICTAL, tell your healthcare provider about all of your medical
1799 conditions, including if you:

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 62

- 1800 • have had a rash or allergic reaction to another antiseizure medicine.
- 1801 • have or have had depression, mood problems, or suicidal thoughts or behavior.
- 1802 • have had aseptic meningitis after taking LAMICTAL or LAMICTAL XR
- 1803 (lamotrigine).
- 1804 • are taking oral contraceptives (birth control pills) or other female hormonal
- 1805 medicines. Do not start or stop taking birth control pills or other female
- 1806 hormonal medicine until you have talked with your healthcare provider. Tell your
- 1807 healthcare provider if you have any changes in your menstrual pattern such as
- 1808 breakthrough bleeding. Stopping these medicines may cause side effects (such
- 1809 as dizziness, lack of coordination, or double vision). Starting these medicines
- 1810 may lessen how well LAMICTAL works.
- 1811 • are pregnant or plan to become pregnant. It is not known if LAMICTAL will harm
- 1812 your unborn baby. If you become pregnant while taking LAMICTAL, talk to your
- 1813 healthcare provider about registering with the North American Antiepileptic Drug
- 1814 Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334.
- 1815 The purpose of this registry is to collect information about the safety of
- 1816 antiepileptic drugs during pregnancy.
- 1817 • are breastfeeding. LAMICTAL passes into breast milk and may cause side effects
- 1818 in a breastfed baby. If you breastfeed while taking LAMICTAL, watch your baby
- 1819 closely for trouble breathing, episodes of temporarily stopping breathing,
- 1820 sleepiness, or poor sucking. Call your baby's healthcare provider right away if
- 1821 you see any of these problems. Talk to your healthcare provider about the best
- 1822 way to feed your baby if you take LAMICTAL.

1823 Tell your healthcare provider about all the medicines you take or if you are planning
1824 to take a new medicine, including prescription and non-prescription medicines,
1825 vitamins, and herbal supplements. If you use LAMICTAL with certain other
1826 medicines, they can affect each other, causing side effects.

1827

1828 **How should I take LAMICTAL?**

- 1829 • Take LAMICTAL exactly as prescribed.
- 1830 • Your healthcare provider may change your dose. Do not change your dose
- 1831 without talking to your healthcare provider.
- 1832 • Do not stop taking LAMICTAL without talking to your healthcare provider.
- 1833 Stopping LAMICTAL suddenly may cause serious problems. For example, if you
- 1834 have epilepsy and you stop taking LAMICTAL suddenly, you may have seizures
- 1835 that do not stop. Talk with your healthcare provider about how to stop
- 1836 LAMICTAL slowly.
- 1837 • If you miss a dose of LAMICTAL, take it as soon as you remember. If it is almost
- 1838 time for your next dose, just skip the missed dose. Take the next dose at your

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 63

- 1839 regular time. **Do not take 2 doses at the same time.**
- 1840 • If you take too much LAMICTAL, call your healthcare provider or your local
- 1841 Poison Control Center or go to the nearest hospital emergency room right away.
- 1842 • If you take too much LAMICTAL, call your healthcare provider or your local
- 1843 Poison Control Center or go to the nearest hospital emergency room right away.
- 1844 • You may not feel the full effect of LAMICTAL for several weeks.
- 1845 • If you have epilepsy, tell your healthcare provider if your seizures get worse or if
- 1846 you have any new types of seizures.
- 1847 • Swallow LAMICTAL Tablets whole.
- 1848 • If you have trouble swallowing LAMICTAL Tablets, tell your healthcare provider
- 1849 because there may be another form of LAMICTAL you can take.
- 1850 • LAMICTAL ODT should be placed on the tongue and moved around the mouth.
- 1851 The tablet will rapidly disintegrate, can be swallowed with or without water, and
- 1852 can be taken with or without food.
- 1853 • LAMICTAL Chewable Dispersible tablets may be swallowed whole, chewed, or
- 1854 mixed in water or diluted fruit juice. If the tablets are chewed, drink a small
- 1855 amount of water or diluted fruit juice to help in swallowing. To break up
- 1856 LAMICTAL Chewable Dispersible tablets, add the tablets to a small amount of
- 1857 liquid (1 teaspoon, or enough to cover the medicine) in a glass or spoon. Wait at
- 1858 least 1 minute or until the tablets are completely broken up, mix the solution
- 1859 together, and take the whole amount right away.
- 1860 • If you receive LAMICTAL in a blisterpack, examine the blisterpack before use. Do
- 1861 not use if blisters are torn, broken, or missing.

1862

1863 **What should I avoid while taking LAMICTAL?**

1864 Do not drive a car or operate complex, hazardous machinery until you know how

1865 LAMICTAL affects you.

1866

1867 **What are the possible side effects of LAMICTAL?**

1868 See "What is the most important information I should know about LAMICTAL?"

1869 Common side effects of LAMICTAL include:

- 1870 • dizziness
- 1871 • tremor
- 1872 • headache
- 1873 • rash
- 1874 • blurred or double vision
- 1875 • fever
- 1876 • lack of coordination

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 64

- 1877 • abdominal pain
- 1878 • sleepiness
- 1879 • back pain
- 1880 • nausea, vomiting
- 1881 • tiredness
- 1882 • insomnia
- 1883 • dry mouth

1884 Tell your healthcare provider about any side effect that bothers you or that does
1885 not go away.

1886 These are not all the possible side effects of LAMICTAL. For more information, ask
1887 your healthcare provider or pharmacist.

1888 Call your doctor for medical advice about side effects. You may report side effects
1889 to FDA at 1-800-FDA-1088.

1890

1891 **How should I store LAMICTAL?**

- 1892 • Store LAMICTAL at room temperature between 68°F and 77°F (20°C and 25°C).
- 1893 • **Keep LAMICTAL and all medicines out of the reach of children.**

1894

1895 **General information about LAMICTAL**

1896 Medicines are sometimes prescribed for purposes other than those listed in a
1897 Medication Guide. Do not use LAMICTAL for a condition for which it was not
1898 prescribed. Do not give LAMICTAL to other people, even if they have the same
1899 symptoms you have. It may harm them.

1900 This Medication Guide summarizes the most important information about
1901 LAMICTAL. If you would like more information, talk with your healthcare provider.
1902 You can ask your healthcare provider or pharmacist for information about
1903 LAMICTAL that is written for healthcare professionals.

1904 For more information, go to www.lamictal.com or call 1-888-825-5249.

1905

1906 **What are the ingredients in LAMICTAL?**

1907 **LAMICTAL Tablets**

1908 Active ingredient: lamotrigine.

1909 Inactive ingredients: lactose; magnesium stearate, microcrystalline cellulose,
1910 povidone, sodium starch glycolate, FD&C Yellow No. 6 Lake (100-mg tablet only),
1911 ferric oxide, yellow (150-mg tablet only), and FD&C Blue No. 2 Lake (200-mg tablet
1912 only).

NDA 020241/S-035 & S-040
NDA 020764/S-028 & S-033
NDA 022251/S-009 & S-002
FDA Approved Labeling Text dated 12/23/2014
Page 65

1913 **LAMICTAL Chewable Dispersible Tablets**

1914 Active ingredient: lamotrigine.

1915 Inactive ingredients: blackcurrant flavor, calcium carbonate, low-substituted
1916 hydroxypropylcellulose, magnesium aluminum silicate, magnesium stearate,
1917 povidone, saccharin sodium, and sodium starch glycolate.

1918 **LAMICTAL ODT Orally Disintegrating Tablets**

1919 Active ingredient: lamotrigine.

1920 Inactive ingredients: artificial cherry flavor, crospovidone, ethylcellulose,
1921 magnesium stearate, mannitol, polyethylene, and sucralose.

1922

1923 **This Medication Guide has been approved by the U.S. Food and Drug**
1924 **Administration.**

1925

1926 LAMICTAL and LAMICTAL ODT are registered trademarks of the GSK group of
1927 companies. The other brands listed are trademarks of their respective owners and
1928 are not trademarks of the GSK group of companies. The makers of these brands
1929 are not affiliated with and do not endorse the GSK group of companies or its
1930 products.

1931

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1933 Distributed by



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1935 GlaxoSmithKline

1936 Research Triangle Park, NC 27709

1937

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1939

1940 December 2014

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FDA Proposed Labeling Text dated 12/23/2014
Page 1

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LAMICTAL XR safely and effectively. See full prescribing information for LAMICTAL XR.

LAMICTAL XR (lamotrigine) Extended-Release 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 and toxic epidermal necrolysis, and/or rash-related death have been caused by lamotrigine. The rate of serious rash is greater in pediatric patients than in adults. Additional factors that may increase the risk of rash include:
 - coadministration with valproate.
 - exceeding recommended initial dose of LAMICTAL XR.
 - exceeding recommended dose escalation for LAMICTAL XR. (5.1)
- Benign rashes are also caused by lamotrigine; 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

Dosage and Administration (2.1, 2.2) 12/2014

INDICATIONS AND USAGE

LAMICTAL XR is an antiepileptic drug (AED) indicated for:

- adjunctive therapy for primary generalized tonic-clonic seizures and partial-onset seizures with or without secondary generalization in patients aged 13 years and older. (1.1)
- conversion to monotherapy in patients aged 13 years and older with partial-onset seizures who are receiving treatment with a single AED. (1.2)

Limitation of use: Safety and effectiveness in patients younger than 13 years have not been established. (1.3)

DOSAGE AND ADMINISTRATION

- Do not exceed the recommended initial dosage and subsequent dose escalation. (2.1)
- Initiation of adjunctive therapy and conversion to monotherapy requires slow titration dependent on concomitant AEDs; the prescriber must refer to the appropriate algorithm in Dosage and Administration. (2.2, 2.3)
 - Adjunct therapy target therapeutic dose range is 200 to 600 mg daily and is dependent on concomitant AEDs. (2.2)
 - Conversion to monotherapy: Target therapeutic dosage range is 250 to 300 mg daily. (2.3)
- Conversion from immediate-release lamotrigine to LAMICTAL XR: The initial dose of LAMICTAL XR should match the total daily dose of the immediate-release lamotrigine. Patients should be closely monitored for seizure control after conversion. (2.4)
- Do not restart LAMICTAL XR in patients who discontinued due to rash unless the potential benefits clearly outweigh the risks. (2.1, 5.1)
- Adjustments to maintenance doses will be necessary in most patients starting or stopping estrogen-containing oral contraceptives. (2.1, 5.7)
- Discontinuation: Taper over a period of at least 2 weeks (approximately 50% dose reduction per week). (2.1, 5.8)

DOSAGE FORMS AND STRENGTHS

Extended-Release Tablets: 25 mg, 50 mg, 100 mg, 200 mg, 250 mg, and 300 mg. (3.1, 16)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Life-threatening serious rash and/or rash-related death: Discontinue at the first sign of rash, unless the rash is clearly not drug related. (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 XR 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. Monitor for signs of anemia, unexpected infection, or bleeding. (5.3)
- Suicidal behavior and ideation: Monitor for suicidal thoughts or behaviors. (5.4)
- Aseptic meningitis: Monitor for signs of meningitis. (5.5)
- Medication errors due to product name confusion: Strongly advise patients to visually inspect tablets to verify the received drug is correct. (3.2, 5.6, 16, 17)

ADVERSE REACTIONS

- Most common adverse reactions with use as adjunctive therapy (treatment difference between LAMICTAL XR and placebo $\geq 4\%$) are dizziness, tremor/intention tremor, vomiting, and diplopia. (6.1)
- Most common adverse reactions with use as monotherapy were similar to those seen with previous trials conducted with immediate-release lamotrigine and LAMICTAL XR. (6.1)

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

DRUG INTERACTIONS

- Valproate increases lamotrigine concentrations more than 2-fold. (7, 12.3)
- Carbamazepine, phenytoin, phenobarbital, primidone, and rifampin decrease lamotrigine concentrations by approximately 40%. (7, 12.3)
- Estrogen-containing oral contraceptives decrease lamotrigine concentrations by approximately 50%. (7, 12.3)
- Protease inhibitors lopinavir/ritonavir and atazanavir/lopinavir decrease lamotrigine exposure by approximately 50% and 32%, respectively. (7, 12.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data may cause fetal harm. (8.1)
- Hepatic impairment: Dosage adjustments required in patients with moderate and severe liver impairment. (2.1, 8.6)
- Renal impairment: Reduced maintenance doses may be effective for patients with significant renal impairment. (2.1, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: SERIOUS SKIN RASHES

1 INDICATIONS AND USAGE

- 1.1 Adjunctive Therapy
- 1.2 Monotherapy
- 1.3 Limitation of Use

2 DOSAGE AND ADMINISTRATION

- 2.1 General Dosing Considerations
- 2.2 Adjunctive Therapy for Primary Generalized Tonic-Clonic and Partial-Onset Seizures
- 2.3 Conversion From Adjunctive Therapy to Monotherapy
- 2.4 Conversion From Immediate-Release Lamotrigine Tablets to LAMICTAL XR

3 DOSAGE FORMS AND STRENGTHS

- 3.1 Extended-Release Tablets
- 3.2 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 Aseptic Meningitis
- 5.6 Potential Medication Errors
- 5.7 Concomitant Use With Oral Contraceptives
- 5.8 Withdrawal Seizures
- 5.9 Status Epilepticus
- 5.10 Sudden Unexplained Death in Epilepsy (SUDEP)
- 5.11 Addition of LAMICTAL XR to a Multidrug Regimen That Includes Valproate
- 5.12 Binding in the Eye and Other Melanin-Containing Tissues
- 5.13 Laboratory Tests

6 ADVERSE REACTIONS

- 6.1 Clinical Trial Experience With LAMICTAL XR for Treatment of Primary Generalized Tonic-Clonic and Partial-Onset Seizures
- 6.2 Other Adverse Reactions Observed During the Clinical Development of Immediate-Release Lamotrigine
- 6.3 Postmarketing Experience With Immediate-Release Lamotrigine

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 Adjunctive Therapy for Primary Generalized Tonic-Clonic Seizures
- 14.2 Adjunctive Therapy for Partial-Onset Seizures
- 14.3 Conversion to Monotherapy for Partial-Onset Seizures

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

1 FULL PRESCRIBING INFORMATION

2
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WARNING: SERIOUS SKIN RASHES

LAMICTAL[®] XR[™] can cause serious rashes requiring hospitalization and discontinuation of treatment. The incidence of these rashes, which have included Stevens-Johnson syndrome, is approximately 0.8% (8 per 1,000) in pediatric patients (aged 2 to 16 years) receiving immediate-release lamotrigine as adjunctive therapy for epilepsy and 0.3% (3 per 1,000) in adults on adjunctive therapy for epilepsy. In a prospectively followed cohort of 1,983 pediatric patients (aged 2 to 16 years) with epilepsy taking adjunctive immediate-release lamotrigine, there was 1 rash-related death. LAMICTAL XR is not approved for patients younger than 13 years. In worldwide postmarketing experience, rare cases of toxic epidermal necrolysis and/or rash-related death have been reported in adult and pediatric patients, but their numbers are too few to permit a precise estimate of the rate.

14 **The risk of serious rash caused by treatment with LAMICTAL XR is not expected**
15 **to differ from that with immediate-release lamotrigine. However, the relatively limited**
16 **treatment experience with LAMICTAL XR makes it difficult to characterize the frequency**
17 **and risk of serious rashes caused by treatment with LAMICTAL XR.**

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

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

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

36 **1 INDICATIONS AND USAGE**

37 **1.1 Adjunctive Therapy**

38 LAMICTAL XR is indicated as adjunctive therapy for primary generalized tonic-clonic
39 (PGTC) seizures and partial-onset seizures with or without secondary generalization in patients
40 aged 13 years and older.

41 **1.2 Monotherapy**

42 LAMICTAL XR is indicated for conversion to monotherapy in patients aged 13 years
43 and older with partial-onset seizures who are receiving treatment with a single antiepileptic drug
44 (AED).

45 Safety and effectiveness of LAMICTAL XR have not been established (1) as initial
46 monotherapy or (2) for simultaneous conversion to monotherapy from 2 or more concomitant
47 AEDs.

48 **1.3 Limitation of Use**

49 Safety and effectiveness of LAMICTAL XR for use in patients younger than 13 years
50 have not been established.

51 **2 DOSAGE AND ADMINISTRATION**

52 LAMICTAL XR Extended-Release Tablets are taken once daily, with or without food.
53 Tablets must be swallowed whole and must not be chewed, crushed, or divided.

54 **2.1 General Dosing Considerations**

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

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

64 LAMICTAL XR Patient Titration Kits provide LAMICTAL XR at doses consistent with
65 the recommended titration schedule for the first 5 weeks of treatment, based upon concomitant
66 medications, for patients with partial-onset seizures and are intended to help reduce the potential
67 for rash. The use of LAMICTAL XR Patient Titration Kits is recommended for appropriate
68 patients who are starting or restarting LAMICTAL XR [see *How Supplied/Storage and Handling*
69 (16)].

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

79 LAMICTAL XR Added to Drugs Known to Induce or Inhibit Glucuronidation:

80 Because lamotrigine is metabolized predominantly by glucuronic acid conjugation, drugs that are
81 known to induce or inhibit glucuronidation may affect the apparent clearance of lamotrigine.
82 Drugs that induce glucuronidation include carbamazepine, phenytoin, phenobarbital, primidone,
83 rifampin, estrogen-containing oral contraceptives, and the protease inhibitors lopinavir/ritonavir
84 and atazanavir/ritonavir. Valproate inhibits glucuronidation. For dosing considerations for
85 LAMICTAL XR in patients on estrogen-containing contraceptives and atazanavir/ritonavir, see
86 below and Table 5. For dosing considerations for LAMICTAL XR in patients on other drugs
87 known to induce or inhibit glucuronidation, see Table 1 and Table 5.

88 Target Plasma Levels: A therapeutic plasma concentration range has not been
89 established for lamotrigine. Dosing of LAMICTAL XR should be based on therapeutic response
90 [see *Clinical Pharmacology (12.3)*].

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

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

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

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

128 (3) *Stopping Estrogen-Containing Oral Contraceptives:* In women not taking
129 carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin and the
130 protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir that induce lamotrigine

131 glucuronidation [see *Drug Interactions (7), Clinical Pharmacology (12.3)*], the maintenance
132 dose of LAMICTAL XR will in most cases need to be decreased by as much as 50% in order to
133 maintain a consistent lamotrigine plasma level. The decrease in dose of LAMICTAL XR should
134 not exceed 25% of the total daily dose per week over a 2-week period, unless clinical response or
135 lamotrigine plasma levels indicate otherwise [see *Clinical Pharmacology (12.3)*]. In women
136 taking LAMICTAL XR in addition to carbamazepine, phenytoin, phenobarbital, primidone, or
137 other drugs such as rifampin and the protease inhibitors lopinavir/ritonavir and
138 atazanavir/ritonavir that induce lamotrigine glucuronidation [see *Drug Interactions (7), Clinical*
139 *Pharmacology (12.3)*], no adjustment to the dose of LAMICTAL XR should be necessary.

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

147 **Patients Taking Atazanavir/Ritonavir:** While atazanavir/ritonavir does reduce the
148 lamotrigine plasma concentration, no adjustments to the recommended dose-escalation
149 guidelines for LAMICTAL XR should be necessary solely based on the use of
150 atazanavir/ritonavir. Dose escalation should follow the recommended guidelines for initiating
151 adjunctive therapy with LAMICTAL XR based on concomitant AED or other concomitant
152 medications (see Tables 1 and 5). In patients already taking maintenance doses of LAMICTAL
153 XR and not taking glucuronidation inducers, the dose of LAMICTAL XR may need to be
154 increased if atazanavir/ritonavir is added, or decreased if atazanavir/ritonavir is discontinued [see
155 *Clinical Pharmacology (12.3)*].

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

164 **Patients With Renal Impairment:** Initial doses of LAMICTAL XR should be based on
165 patients' concomitant medications (see Table 1); reduced maintenance doses may be effective for
166 patients with significant renal impairment [see *Use in Specific Populations (8.7), Clinical*
167 *Pharmacology (12.3)*]. Few patients with severe renal impairment have been evaluated during
168 chronic treatment with immediate-release lamotrigine. Because there is inadequate experience in
169 this population, LAMICTAL XR should be used with caution in these patients.

170 **Discontinuation Strategy:** For patients receiving LAMICTAL XR in combination with
171 other AEDs, a re-evaluation of all AEDs in the regimen should be considered if a change in
172 seizure control or an appearance or worsening of adverse reactions is observed.

173 If a decision is made to discontinue therapy with LAMICTAL XR, a step-wise reduction
174 of dose over at least 2 weeks (approximately 50% per week) is recommended unless safety
175 concerns require a more rapid withdrawal [*see Warnings and Precautions (5.8)*].

176 Discontinuing carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such
177 as rifampin and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir that induce
178 lamotrigine glucuronidation should prolong the half-life of lamotrigine; discontinuing valproate
179 should shorten the half-life of lamotrigine.

180 **2.2 Adjunctive Therapy for Primary Generalized Tonic-Clonic and Partial-Onset**
181 **Seizures**

182 This section provides specific dosing recommendations for patients aged 13 years and
183 older. Specific dosing recommendations are provided depending upon concomitant AEDs or
184 other concomitant medications.

185
186

Table 1. Escalation Regimen for LAMICTAL XR in Patients Aged 13 Years and Older

	In Patients TAKING Valproate^a	In Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone,^b or Valproate^a	In Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone^b and NOT TAKING Valproate^a
Weeks 1 and 2	25 mg every <i>other</i> day	25 mg every day	50 mg every day
Weeks 3 and 4	25 mg every day	50 mg every day	100 mg every day
Week 5	50 mg every day	100 mg every day	200 mg every day
Week 6	100 mg every day	150 mg every day	300 mg every day
Week 7	150 mg every day	200 mg every day	400 mg every day
Maintenance range (week 8 and onward)	200 to 250 mg every day ^c	300 to 400 mg every day ^c	400 to 600 mg every day ^c

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

189 ^b Drugs that induce lamotrigine glucuronidation and increase clearance, other than the specified
190 antiepileptic drugs, include estrogen-containing oral contraceptives, rifampin, and the protease
191 inhibitors lopinavir/ritonavir and atazanavir/ritonavir. Dosing recommendations for oral
192 contraceptives and the protease inhibitor atazanavir/ritonavir can be found in General Dosing
193 Considerations [*see Dosage and Administration (2.1)*]. Patients on rifampin and the protease
194 inhibitor lopinavir/ritonavir should follow the same dosing titration/maintenance regimen used

195 with antiepileptic drugs that induce glucuronidation and increase clearance [see *Dosage and*
196 *Administration (2.1), Drug Interactions (7), and Clinical Pharmacology (12.3)*].
197 ^c Dose increases at week 8 or later should not exceed 100 mg daily at weekly intervals.
198

199 **2.3 Conversion From Adjunctive Therapy to Monotherapy**

200 The goal of the transition regimen is to attempt to maintain seizure control while
201 mitigating the risk of serious rash associated with the rapid titration of LAMICTAL XR.

202 To avoid an increased risk of rash, the recommended maintenance dosage range of
203 LAMICTAL XR as monotherapy is 250 to 300 mg given once daily.

204 The recommended initial dose and subsequent dose escalations for LAMICTAL XR
205 should not be exceeded [see *Boxed Warning*].

206 Conversion From Adjunctive Therapy With Carbamazepine, Phenytoin,
207 Phenobarbital, or Primidone to Monotherapy With LAMICTAL XR: After achieving a dose
208 of 500 mg/day of LAMICTAL XR using the guidelines in Table 1, the concomitant enzyme-
209 inducing AED should be withdrawn by 20% decrements each week over a 4-week period. Two
210 weeks after completion of withdrawal of the enzyme-inducing AED, the dosage of
211 LAMICTAL XR may be decreased no faster than 100 mg/day each week to achieve the
212 monotherapy maintenance dosage range of 250 to 300 mg/day.

213 The regimen for the withdrawal of the concomitant AED is based on experience gained in
214 the controlled monotherapy clinical trial using immediate-release lamotrigine.

215 Conversion From Adjunctive Therapy With Valproate to Monotherapy With
216 LAMICTAL XR: The conversion regimen involves the 4 steps outlined in Table 2.
217

218 **Table 2. Conversion From Adjunctive Therapy With Valproate to Monotherapy With**
219 **LAMICTAL XR in Patients Aged 13 Years and Older With Epilepsy**

	LAMICTAL XR	Valproate
Step 1	Achieve a dose of 150 mg/day according to guidelines in Table 1.	Maintain established stable dose.
Step 2	Maintain at 150 mg/day.	Decrease dose by decrements no greater than 500 mg/day/week to 500 mg/day and then maintain for 1 week.
Step 3	Increase to 200 mg/day.	Simultaneously decrease to 250 mg/day and maintain for 1 week.
Step 4	Increase to 250 or 300 mg/day.	Discontinue.

220
221 Conversion From Adjunctive Therapy With Antiepileptic Drugs Other Than
222 Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate to Monotherapy
223 With LAMICTAL XR: After achieving a dosage of 250 to 300 mg/day of LAMICTAL XR using
224 the guidelines in Table 1, the concomitant AED should be withdrawn by 20% decrements each

225 week over a 4-week period. No adjustment to the monotherapy dose of LAMICTAL XR is
226 needed.

227 **2.4 Conversion From Immediate-Release Lamotrigine Tablets to LAMICTAL XR**

228 Patients may be converted directly from immediate-release lamotrigine to LAMICTAL
229 XR Extended-Release Tablets. The initial dose of LAMICTAL XR should match the total daily
230 dose of immediate-release lamotrigine. However, some subjects on concomitant enzyme-
231 inducing agents may have lower plasma levels of lamotrigine on conversion and should be
232 monitored [*see Clinical Pharmacology (12.3)*].

233 Following conversion to LAMICTAL XR, all patients (but especially those on drugs that
234 induce lamotrigine glucuronidation) should be closely monitored for seizure control [*see Drug*
235 *Interactions (7)*]. Depending on the therapeutic response after conversion, the total daily dose
236 may need to be adjusted within the recommended dosing instructions (Table 1).

237 **3 DOSAGE FORMS AND STRENGTHS**

238 **3.1 Extended-Release Tablets**

239 25 mg, yellow with white center, round, biconvex, film-coated tablets printed with
240 “LAMICTAL” and “XR 25.”

241 50 mg, green with white center, round, biconvex, film-coated tablets printed with
242 “LAMICTAL” and “XR 50.”

243 100 mg, orange with white center, round, biconvex, film-coated tablets printed with
244 “LAMICTAL” and “XR 100.”

245 200 mg, blue with white center, round, biconvex, film-coated tablets printed with
246 “LAMICTAL” and “XR 200.”

247 250 mg, purple with white center, caplet-shaped, film-coated tablets printed with
248 “LAMICTAL” and “XR 250.”

249 300 mg, gray with white center, caplet-shaped, film-coated tablets printed with
250 “LAMICTAL” and “XR 300.”

251 **3.2 Potential Medication Errors**

252 Patients should be strongly advised to visually inspect their tablets to verify that they are
253 receiving LAMICTAL XR, as opposed to other medications, and that they are receiving the
254 correct formulation of lamotrigine each time they fill their prescription. Depictions of the
255 LAMICTAL XR tablets can be found in the Medication Guide.

256 **4 CONTRAINDICATIONS**

257 LAMICTAL XR is contraindicated in patients who have demonstrated hypersensitivity
258 (e.g., rash, angioedema, acute urticaria, extensive pruritus, mucosal ulceration) to the drug or its
259 ingredients [*see Boxed Warning, Warnings and Precautions (5.1, 5.2)*].

260 **5 WARNINGS AND PRECAUTIONS**

261 **5.1 Serious Skin Rashes [*see Boxed Warning*]**

262 The risk of serious rash caused by treatment with LAMICTAL XR is not expected to
263 differ from that with immediate-release lamotrigine [*see Boxed Warning*]. However, the
264 relatively limited treatment experience with LAMICTAL XR makes it difficult to characterize
265 the frequency and risk of serious rashes caused by treatment with LAMICTAL XR.

266 **Pediatric Population:** The incidence of serious rash associated with hospitalization and
267 discontinuation of immediate-release lamotrigine in a prospectively followed cohort of pediatric
268 patients (aged 2 to 16 years) with epilepsy receiving adjunctive therapy with immediate-release
269 lamotrigine was approximately 0.8% (16 of 1,983). When 14 of these cases were reviewed by 3
270 expert dermatologists, there was considerable disagreement as to their proper classification. To
271 illustrate, one dermatologist considered none of the cases to be Stevens-Johnson syndrome;
272 another assigned 7 of the 14 to this diagnosis. There was 1 rash-related death in this
273 1,983-patient cohort. Additionally, there have been rare cases of toxic epidermal necrolysis with
274 and without permanent sequelae and/or death in US and foreign postmarketing experience.

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

279 LAMICTAL XR is not approved in patients younger than 13 years.

280 **Adult Population:** Serious rash associated with hospitalization and discontinuation of
281 immediate-release lamotrigine occurred in 0.3% (11 of 3,348) of adult patients who received
282 immediate-release lamotrigine in premarketing clinical trials of epilepsy. In worldwide
283 postmarketing experience, rare cases of rash-related death have been reported, but their numbers
284 are too few to permit a precise estimate of the rate.

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

288 There is evidence that the inclusion of valproate in a multidrug regimen increases the risk
289 of serious, potentially life-threatening rash in adults. Specifically, of 584 patients administered
290 immediate-release lamotrigine with valproate in epilepsy clinical trials, 6 (1%) were hospitalized
291 in association with rash; in contrast, 4 (0.16%) of 2,398 clinical trial patients and volunteers
292 administered immediate-release lamotrigine in the absence of valproate were hospitalized.

293 **Patients With History of Allergy or Rash to Other Antiepileptic Drugs:** The risk of
294 nonserious rash may be increased when the recommended initial dose and/or the rate of dose
295 escalation for LAMICTAL XR is exceeded and in patients with a history of allergy or rash to
296 other AEDs.

297 **5.2 Multiorgan Hypersensitivity Reactions and Organ Failure**

298 Multiorgan hypersensitivity reactions, also known as drug reaction with eosinophilia and
299 systemic symptoms (DRESS), have occurred with lamotrigine. Some have been fatal or life
300 threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or
301 lymphadenopathy in association with other organ system involvement, such as hepatitis,

302 nephritis, hematologic abnormalities, myocarditis, or myositis, sometimes resembling an acute
303 viral infection. Eosinophilia is often present. This disorder is variable in its expression and other
304 organ systems not noted here may be involved.

305 Fatalities associated with acute multiorgan failure and various degrees of hepatic failure
306 have been reported in 2 of 3,796 adult patients and 4 of 2,435 pediatric patients who received
307 lamotrigine in epilepsy clinical trials. Rare fatalities from multiorgan failure have also been
308 reported in postmarketing use.

309 Isolated liver failure without rash or involvement of other organs has also been reported
310 with lamotrigine.

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

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

319 **5.3 Blood Dyscrasias**

320 There have been reports of blood dyscrasias with immediate-release lamotrigine that may
321 or may not be associated with multiorgan hypersensitivity (also known as DRESS) [*see*
322 *Warnings and Precautions (5.2)*]. These have included neutropenia, leukopenia, anemia,
323 thrombocytopenia, pancytopenia, and, rarely, aplastic anemia and pure red cell aplasia.

324 **5.4 Suicidal Behavior and Ideation**

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

329 Pooled analyses of 199 placebo-controlled clinical trials (monotherapy and adjunctive
330 therapy) of 11 different AEDs showed that patients randomized to 1 of the AEDs had
331 approximately twice the risk (adjusted Relative Risk 1.8, 95% CI: 1.2, 2.7) of suicidal thinking
332 or behavior compared with patients randomized to placebo. In these trials, which had a median
333 treatment duration of 12 weeks, the estimated incidence of suicidal behavior or ideation among
334 27,863 AED-treated patients was 0.43%, compared with 0.24% among 16,029 placebo-treated
335 patients, representing an increase of approximately 1 case of suicidal thinking or behavior for
336 every 530 patients treated. There were 4 suicides in drug-treated patients in the trials and none in
337 placebo-treated patients, but the number of events is too small to allow any conclusion about
338 drug effect on suicide.

339 The increased risk of suicidal thoughts or behavior with AEDs was observed as early as
340 1 week after starting treatment with AEDs and persisted for the duration of treatment assessed.

341 Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal
342 thoughts or behavior beyond 24 weeks could not be assessed.

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

347 Table 3 shows absolute and relative risk by indication for all evaluated AEDs.

348

349 **Table 3. 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

350

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

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

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

365 **5.5 Aseptic Meningitis**

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

369 Postmarketing cases of aseptic meningitis have been reported in pediatric and adult
370 patients taking lamotrigine for various indications. Symptoms upon presentation have included
371 headache, fever, nausea, vomiting, and nuchal rigidity. Rash, photophobia, myalgia, chills,

372 altered consciousness, and somnolence were also noted in some cases. Symptoms have been
373 reported to occur within 1 day to one and a half months following the initiation of treatment. In
374 most cases, symptoms were reported to resolve after discontinuation of lamotrigine. Re-exposure
375 resulted in a rapid return of symptoms (from within 30 minutes to 1 day following re-initiation of
376 treatment) that were frequently more severe. Some of the patients treated with lamotrigine who
377 developed aseptic meningitis had underlying diagnoses of systemic lupus erythematosus or other
378 autoimmune diseases.

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

387 **5.6 Potential Medication Errors**

388 Medication errors involving LAMICTAL have occurred. In particular, the names
389 LAMICTAL or lamotrigine can be confused with the names of other commonly used
390 medications. Medication errors may also occur between the different formulations of
391 LAMICTAL. To reduce the potential of medication errors, write and say LAMICTAL XR
392 clearly. Depictions of the LAMICTAL XR Extended-Release Tablets can be found in the
393 Medication Guide. Each LAMICTAL XR tablet has a distinct color and white center, and is
394 printed with “LAMICTAL XR” and the tablet strength. These distinctive features serve to
395 identify the different presentations of the drug and thus may help reduce the risk of medication
396 errors. LAMICTAL XR is supplied in round, unit-of-use bottles with orange caps containing
397 30 tablets. The label on the bottle includes a depiction of the tablets that further communicates to
398 patients and pharmacists that the medication is LAMICTAL XR and the specific tablet strength
399 included in the bottle. The unit-of-use bottle with a distinctive orange cap and distinctive bottle
400 label features serves to identify the different presentations of the drug and thus may help to
401 reduce the risk of medication errors. To avoid the medication error of using the wrong drug or
402 formulation, patients should be strongly advised to visually inspect their tablets to verify that
403 they are LAMICTAL XR each time they fill their prescription.

404 **5.7 Concomitant Use With Oral Contraceptives**

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

412 **5.8 Withdrawal Seizures**

413 As with other AEDs, LAMICTAL XR should not be abruptly discontinued. In patients
414 with epilepsy there is a possibility of increasing seizure frequency. Unless safety concerns
415 require a more rapid withdrawal, the dose of LAMICTAL XR should be tapered over a period of
416 at least 2 weeks (approximately 50% reduction per week) [*see Dosage and Administration*
417 (2.1)].

418 **5.9 Status Epilepticus**

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

425 **5.10 Sudden Unexplained Death in Epilepsy (SUDEP)**

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

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

444 **5.11 Addition of LAMICTAL XR to a Multidrug Regimen That Includes Valproate**

445 Because valproate reduces the clearance of lamotrigine, the dosage of lamotrigine in the
446 presence of valproate is less than half of that required in its absence [*see Dosage and*
447 *Administration (2.1, 2.2), Drug Interactions (7)*].

448 **5.12 Binding in the Eye and Other Melanin-Containing Tissues**

449 Because lamotrigine binds to melanin, it could accumulate in melanin-rich tissues over
450 time. This raises the possibility that lamotrigine may cause toxicity in these tissues after
451 extended use. Although ophthalmological testing was performed in 1 controlled clinical trial, the

452 testing was inadequate to exclude subtle effects or injury occurring after long-term exposure.
453 Moreover, the capacity of available tests to detect potentially adverse consequences, if any, of
454 lamotrigine's binding to melanin is unknown.

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

458 **5.13 Laboratory Tests**

459 Plasma Concentrations of Lamotrigine: The value of monitoring plasma
460 concentrations of lamotrigine in patients treated with LAMICTAL XR has not been established.
461 Because of the possible pharmacokinetic interactions between lamotrigine and other drugs,
462 including AEDs (see Table 6), monitoring of the plasma levels of lamotrigine and concomitant
463 drugs may be indicated, particularly during dosage adjustments. In general, clinical judgment
464 should be exercised regarding monitoring of plasma levels of lamotrigine and other drugs and
465 whether or not dosage adjustments are necessary.

466 Effect on Leukocytes: Treatment with LAMICTAL XR caused an increased incidence
467 of subnormal (below the reference range) values in some hematology analytes (e.g., total white
468 blood cells, monocytes). The treatment effect (LAMICTAL XR % - Placebo %) incidence of
469 subnormal counts was 3% for total white blood cells and 4% for monocytes.

470 **6 ADVERSE REACTIONS**

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

- 473 • Serious skin rashes [*see Warnings and Precautions (5.1)*]
- 474 • Multiorgan hypersensitivity reactions and organ failure [*see Warnings and Precautions (5.2)*]
- 475 • Blood dyscrasias [*see Warnings and Precautions (5.3)*]
- 476 • Suicidal behavior and ideation [*see Warnings and Precautions (5.4)*]
- 477 • Aseptic meningitis [*see Warnings and Precautions (5.5)*]
- 478 • Withdrawal seizures [*see Warnings and Precautions (5.8)*]
- 479 • Status epilepticus [*see Warnings and Precautions (5.9)*]
- 480 • Sudden unexplained death in epilepsy [*see Warnings and Precautions (5.10)*]

481 **6.1 Clinical Trial Experience With LAMICTAL XR for Treatment of Primary** 482 **Generalized Tonic-Clonic and Partial-Onset Seizures**

483 Most Common Adverse Reactions in Clinical Trials: *Adjunctive Therapy in*
484 *Patients With Epilepsy:* Because clinical trials are conducted under widely varying conditions,
485 adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with
486 rates in the clinical trials of another drug and may not reflect the rates observed in practice.

487 LAMICTAL XR has been evaluated for safety in patients aged 13 years and older with
488 PGTC and partial-onset seizures. The most commonly observed adverse reactions in these 2
489 double-blind, placebo-controlled trials of adjunctive therapy with LAMICTAL XR were, in

490 order of decreasing incidence (treatment difference between LAMICTAL XR and placebo $\geq 4\%$):
491 dizziness, tremor/intention tremor, vomiting, and diplopia.

492 In these 2 trials, adverse reactions led to withdrawal of 4 (2%) patients in the group
493 receiving placebo and 10 (5%) patients in the group receiving LAMICTAL XR. Dizziness was
494 the most common reason for withdrawal in the group receiving LAMICTAL XR (5 patients
495 [3%]). The next most common adverse reactions leading to withdrawal in 2 patients each (1%)
496 were rash, headache, nausea, and nystagmus.

497 Table 4 displays the incidence of adverse reactions in these two 19-week, double-blind,
498 placebo-controlled trials of patients with PGTC and partial onset seizures.

499

500 **Table 4. Adverse Reaction Incidence in Double-Blind, Placebo-Controlled Adjunctive**
501 **Trials in Patients With Epilepsy (Adverse reactions $\geq 2\%$ of patients treated with**
502 **LAMICTAL XR and numerically more frequent than in the placebo group.)**

Body System/ Adverse Reaction	Percent of Patients Receiving Adjunctive LAMICTAL XR (n = 190)	Percent of Patients Receiving Adjunctive Placebo (n = 195)
Ear and labyrinth disorders Vertigo	3	<1
Eye disorders Diplopia Vision blurred	5 3	<1 2
Gastrointestinal disorders Nausea Vomiting Diarrhea Constipation Dry mouth	7 6 5 2 2	4 3 3 <1 1
General disorders and administration site conditions Asthenia and fatigue	6	4
Infections and infestations Sinusitis	2	1
Metabolic and nutritional disorders Anorexia	3	2
Musculoskeletal and connective tissue disorder Myalgia	2	0

Nervous system		
Dizziness	14	6
Tremor and intention tremor	6	1
Somnolence	5	3
Cerebellar coordination and balance disorder	3	0
Nystagmus	2	<1
Psychiatric disorders		
Depression	3	<1
Anxiety	3	0
Respiratory, thoracic, and mediastinal disorders		
Pharyngolaryngeal pain	3	2
Vascular disorder		
Hot flush	2	0

503 Note: In these trials the incidence of nonserious rash was 2% for LAMICTAL XR and 3% for
504 placebo. In clinical trials evaluating immediate-release lamotrigine, the rate of serious rash was
505 0.3% in adults on adjunctive therapy for epilepsy [*see Boxed Warning*].
506

507 Adverse reactions were also analyzed to assess the incidence of the onset of an event in
508 the titration period, and in the maintenance period, and if adverse reactions occurring in the
509 titration phase persisted in the maintenance phase.

510 The incidence for many adverse reactions caused by treatment with LAMICTAL XR was
511 increased relative to placebo (i.e., treatment difference between LAMICTAL XR and placebo
512 $\geq 2\%$) in either the titration or maintenance phases of the trial. During the titration phase, an
513 increased incidence (shown in descending order of % treatment difference) was observed for
514 diarrhea, nausea, vomiting, somnolence, vertigo, myalgia, hot flush, and anxiety. During the
515 maintenance phase, an increased incidence was observed for dizziness, tremor, and diplopia.
516 Some adverse reactions developing in the titration phase were notable for persisting (>7 days)
517 into the maintenance phase. These persistent adverse reactions included somnolence and
518 dizziness.

519 There were inadequate data to evaluate the effect of dose and/or concentration on the
520 incidence of adverse reactions because, although patients were randomized to different target
521 doses based upon concomitant AEDs, the plasma exposure was expected to be generally similar
522 among all patients receiving different doses. However, in a randomized, parallel trial comparing
523 placebo with 300 and 500 mg/day of immediate-release lamotrigine, the incidence of the most
524 common adverse reactions ($\geq 5\%$) such as ataxia, blurred vision, diplopia, and dizziness were
525 dose related. Less common adverse reactions (<5%) were not assessed for dose-response
526 relationships.

527 *Monotherapy in Patients With Epilepsy:* Adverse reactions observed in this trial
528 were generally similar to those observed and attributed to drug in adjunctive and monotherapy
529 immediate-release lamotrigine and adjunctive LAMICTAL XR placebo-controlled trials. Only 2
530 adverse events, nasopharyngitis and upper respiratory tract infection, were observed at a rate of
531 $\geq 3\%$ and not reported at a similar rate in previous trials. Because this trial did not include a
532 placebo control group, causality could not be established [see *Clinical Studies (14.3)*].

533 **6.2 Other Adverse Reactions Observed During the Clinical Development of** 534 **Immediate-Release Lamotrigine**

535 All reported reactions are included except those already listed in the previous tables or
536 elsewhere in the labeling, those too general to be informative, and those not reasonably
537 associated with the use of the drug.

538 Adjunctive Therapy in Adults With Epilepsy: In addition to the adverse reactions
539 reported above from the development of LAMICTAL XR, the following adverse reactions with
540 an uncertain relationship to lamotrigine were reported during the clinical development of
541 immediate-release lamotrigine for treatment of epilepsy in adults. These reactions occurred in
542 $\geq 2\%$ of patients receiving immediate-release lamotrigine and more frequently than in the placebo
543 group.

544 *Body as a Whole:* Headache, flu syndrome, fever, neck pain.

545 *Musculoskeletal:* Arthralgia.

546 *Nervous:* Insomnia, convulsion, irritability, speech disorder, concentration
547 disturbance.

548 *Respiratory:* Pharyngitis, cough increased.

549 *Skin and Appendages:* Rash, pruritus.

550 *Urogenital (female patients only):* Vaginitis, amenorrhea, dysmenorrhea.

551 Monotherapy in Adults With Epilepsy: In addition to the adverse reactions reported
552 above from the development of LAMICTAL XR, the following adverse reactions with an
553 uncertain relationship to lamotrigine were reported during the clinical development of
554 immediate-release lamotrigine for treatment of epilepsy in adults. These reactions occurred in
555 $> 2\%$ of patients receiving immediate-release lamotrigine and more frequently than in the placebo
556 group.

557 *Body as a Whole:* Chest pain.

558 *Digestive:* Rectal hemorrhage, peptic ulcer.

559 *Metabolic and Nutritional:* Weight decrease, peripheral edema.

560 *Nervous:* Hypesthesia, libido increase, decreased reflexes.

561 *Respiratory:* Epistaxis, dyspnea.

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

563 *Special Senses:* Vision abnormality.

564 *Urogenital (female patients only):* Dysmenorrhea.

565 Other Clinical Trial Experience: Immediate-release lamotrigine has been administered
566 to 6,694 individuals for whom complete adverse reaction data was captured during all clinical
567 trials, only some of which were placebo controlled.

568 Adverse reactions are further classified within body system categories and enumerated in
569 order of decreasing frequency using the following definitions: *frequent* adverse reactions are
570 defined as those occurring in at least 1/100 patients; *infrequent* adverse reactions are those
571 occurring in 1/100 to 1/1,000 patients; *rare* adverse reactions are those occurring in fewer than
572 1/1,000 patients.

573 *Cardiovascular System: Infrequent:* Hypertension, palpitations, postural
574 hypotension, syncope, tachycardia, vasodilation.

575 *Dermatological: Infrequent:* Acne, alopecia, hirsutism, maculopapular rash, urticaria.
576 *Rare:* Leukoderma, multiforme erythema, petechial rash, pustular rash.

577 *Digestive System: Infrequent:* Dysphagia, liver function tests abnormal, mouth
578 ulceration. *Rare:* Gastrointestinal hemorrhage, hemorrhagic colitis, hepatitis, melena and
579 stomach ulcer.

580 *Endocrine System: Rare:* Goiter, hypothyroidism.

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

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

587 *Musculoskeletal System: Rare:* Muscle atrophy, pathological fracture, tendinous
588 contracture.

589 *Nervous System: Frequent:* Confusion. *Infrequent:* Akathisia, apathy, aphasia,
590 depersonalization, dysarthria, dyskinesia, euphoria, hallucinations, hostility, hyperkinesia,
591 hypertonia, libido decreased, memory decrease, mind racing, movement disorder, myoclonus,
592 panic attack, paranoid reaction, personality disorder, psychosis, stupor. *Rare:* Choreoathetosis,
593 delirium, delusions, dysphoria, dystonia, extrapyramidal syndrome, hemiplegia, hyperalgesia,
594 hyperesthesia, hypokinesia, hypotonia, manic depression reaction, neuralgia, paralysis,
595 peripheral neuritis.

596 *Respiratory System: Rare:* Hiccup, hyperventilation.

597 *Special Senses: Frequent:* Amblyopia. *Infrequent:* Abnormality of
598 accommodation, conjunctivitis, dry eyes, ear pain, photophobia, taste perversion, tinnitus. *Rare:*
599 Deafness, lacrimation disorder, oscillopsia, parosmia, ptosis, strabismus, taste loss, uveitis, visual
600 field defect.

601 *Urogenital System: Infrequent:* Abnormal ejaculation, hematuria, impotence,
602 menorrhagia, polyuria, urinary incontinence. *Rare:* Acute kidney failure, breast neoplasm,
603 creatinine increase, female lactation, kidney failure, kidney pain, nocturia, urinary retention,
604 urinary urgency.

605 **6.3 Postmarketing Experience With Immediate-Release Lamotrigine**

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

611 Blood and Lymphatic: Agranulocytosis, hemolytic anemia, lymphadenopathy not
612 associated with hypersensitivity disorder.

613 Gastrointestinal: Esophagitis.

614 Hepatobiliary Tract and Pancreas: Pancreatitis.

615 Immunologic: Lupus-like reaction, vasculitis.

616 Lower Respiratory: Apnea.

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

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

621 Non-site Specific: Progressive immunosuppression.

622 **7 DRUG INTERACTIONS**

623 Significant drug interactions with lamotrigine are summarized in Table 5. Additional
624 details of these drug interaction studies, which were conducted using immediate-release
625 lamotrigine, are provided in the Clinical Pharmacology section [*see Clinical Pharmacology*
626 (12.3)].

627

NDA 022115/S-004 & S-014
FDA Proposed Labeling Text dated 12/23/2014
Page 21

628 **Table 5. Established and Other Potentially Significant Drug Interactions**

Concomitant Drug	Effect on Concentration of Lamotrigine or Concomitant Drug	Clinical Comment
Estrogen-containing oral contraceptive preparations containing 30 mcg ethinylestradiol and 150 mcg levonorgestrel	↓ lamotrigine ↓ levonorgestrel	Decreased lamotrigine concentrations approximately 50%. Decrease in levonorgestrel component by 19%.
Carbamazepine and carbamazepine epoxide	↓ lamotrigine ? carbamazepine epoxide	Addition of carbamazepine decreases lamotrigine concentration approximately 40%. May increase carbamazepine epoxide levels.
Lopinavir/ritonavir	↓ lamotrigine	Decreased lamotrigine concentration approximately 50%.
Atazanavir/ritonavir	↓ lamotrigine	Decreased lamotrigine AUC approximately 32%.
Phenobarbital/primidone	↓ lamotrigine	Decreased lamotrigine concentration approximately 40%.
Phenytoin	↓ lamotrigine	Decreased lamotrigine concentration approximately 40%.
Rifampin	↓ lamotrigine	Decreased lamotrigine AUC approximately 40%.
Valproate	↑ lamotrigine ? valproate	Increased lamotrigine concentrations slightly more than 2-fold. There are conflicting study results regarding effect of lamotrigine on valproate concentrations: 1) a mean 25% decrease in valproate concentrations in healthy volunteers, 2) no change in valproate concentrations in controlled clinical trials in patients with epilepsy.

629 ↓ = Decreased (induces lamotrigine glucuronidation).

630 ↑ = Increased (inhibits lamotrigine glucuronidation).

631 ? = Conflicting data.

632 **8 USE IN SPECIFIC POPULATIONS**

633 **8.1 Pregnancy**

634 Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled
635 trials in pregnant women. In animal studies, lamotrigine was developmentally toxic at doses
636 lower than those administered clinically. LAMICTAL XR should be used during pregnancy only
637 if the potential benefit justifies the potential risk to the fetus.

638 When lamotrigine was administered to pregnant mice, rats, or rabbits during the period of
639 organogenesis (oral doses of up to 125, 25, and 30 mg/kg, respectively), reduced fetal body
640 weight and increased incidences of fetal skeletal variations were seen in mice and rats at doses
641 that were also maternally toxic. The no-effect doses for embryo-fetal developmental toxicity in
642 mice, rats, and rabbits (75, 6.25, and 30 mg/kg, respectively) are similar to (mice and rabbits) or
643 less than the human dose of 400 mg/day on a body surface area (mg/m²) basis.

644 In a study in which pregnant rats were administered lamotrigine (oral doses of 5 or
645 25 mg/kg) during the period of organogenesis and offspring were evaluated postnatally,
646 behavioral abnormalities were observed in exposed offspring at both doses. The lowest effect
647 dose for developmental neurotoxicity in rats is less than the human dose of 400 mg/day on a
648 mg/m² basis. Maternal toxicity was observed at the higher dose tested.

649 When pregnant rats were administered lamotrigine (oral doses of 5, 10, or 20 mg/kg)
650 during the latter part of gestation, increased offspring mortality (including stillbirths) was seen at
651 all doses. The lowest effect dose for peri/postnatal developmental toxicity in rats is less than the
652 human dose of 400 mg/day on a mg/m² basis. Maternal toxicity was observed at the 2 highest
653 doses tested.

654 Lamotrigine decreases fetal folate concentrations in rat, an effect known to be associated
655 with adverse pregnancy outcomes in animals and humans.

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

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

667 **8.2 Labor and Delivery**

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

669 **8.3 Nursing Mothers**

670 Lamotrigine is present in milk from lactating women taking LAMICTAL XR. Data from
671 multiple small studies indicate that lamotrigine plasma levels in human milk-fed infants have

NDA 022115/S-004 & S-014
FDA Proposed Labeling Text dated 12/23/2014
Page 23

712 **8.6 Patients With Hepatic Impairment**

713 Experience in patients with hepatic impairment is limited. Based on a clinical
714 pharmacology study with immediate-release lamotrigine in 24 subjects with mild, moderate, and
715 severe liver impairment [see *Clinical Pharmacology (12.3)*], the following general
716 recommendations can be made. No dosage adjustment is needed in patients with mild liver
717 impairment. Initial, escalation, and maintenance doses should generally be reduced by
718 approximately 25% in patients with moderate and severe liver impairment without ascites and
719 50% in patients with severe liver impairment with ascites. Escalation and maintenance doses
720 may be adjusted according to clinical response [see *Dosage and Administration (2.1)*].

721 **8.7 Patients With Renal Impairment**

722 Lamotrigine is metabolized mainly by glucuronic acid conjugation, with the majority of
723 the metabolites being recovered in the urine. In a small study comparing a single dose of
724 immediate-release lamotrigine in subjects with varying degrees of renal impairment with healthy
725 volunteers, the plasma half-life of lamotrigine was approximately twice as long in the subjects
726 with chronic renal failure [see *Clinical Pharmacology (12.3)*].

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

732 **10 OVERDOSAGE**

733 **10.1 Human Overdose Experience**

734 Overdoses involving quantities up to 15 g have been reported for immediate-release
735 lamotrigine, some of which have been fatal. Overdose has resulted in ataxia, nystagmus, seizures
736 (including tonic-clonic seizures), decreased level of consciousness, coma, and intraventricular
737 conduction delay.

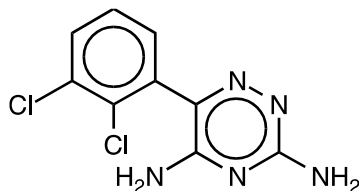
738 **10.2 Management of Overdose**

739 There are no specific antidotes for lamotrigine. Following a suspected overdose,
740 hospitalization of the patient is advised. General supportive care is indicated, including frequent
741 monitoring of vital signs and close observation of the patient. If indicated, emesis should be
742 induced; usual precautions should be taken to protect the airway. It is uncertain whether
743 hemodialysis is an effective means of removing lamotrigine from the blood. In 6 renal failure
744 patients, about 20% of the amount of lamotrigine in the body was removed by hemodialysis
745 during a 4-hour session. A Poison Control Center should be contacted for information on the
746 management of overdosage of LAMICTAL XR.

747 **11 DESCRIPTION**

748 LAMICTAL XR (lamotrigine), an AED of the phenyltriazine class, is chemically
749 unrelated to existing AEDs. Lamotrigine's chemical name is 3,5-diamino-6-(2,3-
750 dichlorophenyl)-*as*-triazine, its molecular formula is C₉H₇N₅Cl₂, and its molecular weight is

751 256.09. Lamotrigine is a white to pale cream-colored powder and has a pK_a of 5.7. Lamotrigine
752 is very slightly soluble in water (0.17 mg/mL at 25°C) and slightly soluble in 0.1 M HCl
753 (4.1 mg/mL at 25°C). The structural formula is:
754



755
756

757 LAMICTAL XR Extended-Release Tablets are supplied for oral administration as 25-mg
758 (yellow with white center), 50-mg (green with white center), 100-mg (orange with white center),
759 200-mg (blue with white center), 250-mg (purple with white center), and 300-mg (gray with
760 white center) tablets. Each tablet contains the labeled amount of lamotrigine and the following
761 inactive ingredients: glycerol monostearate, hypromellose, lactose monohydrate; magnesium
762 stearate; methacrylic acid copolymer dispersion, polyethylene glycol 400, polysorbate 80, silicon
763 dioxide (25- and 50-mg tablets only), titanium dioxide, triethyl citrate, carmine (250-mg tablet
764 only), iron oxide black (50-, 250-, and 300-mg tablets only), iron oxide yellow (25-, 50-, and
765 100-mg tablets only), iron oxide red (100-mg tablet only), FD&C Blue No. 2 Aluminum Lake
766 (200- and 250-mg tablets only). Tablets are printed with edible black ink.

767 LAMICTAL XR Extended-Release Tablets contain a modified-release eroding
768 formulation as the core. The tablets are coated with a clear enteric coat and have an aperture
769 drilled through the coats on both faces of the tablet (DiffCORE™) to enable a controlled release
770 of drug in the acidic environment of the stomach. The combination of this and the modified-
771 release core are designed to control the dissolution rate of lamotrigine over a period of
772 approximately 12 to 15 hours, leading to a gradual increase in serum lamotrigine levels.

773 12 CLINICAL PHARMACOLOGY

774 12.1 Mechanism of Action

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

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

787 Effect of Lamotrigine on N-Methyl d-Aspartate-Receptor Mediated Activity:
788 Lamotrigine did not inhibit N-methyl d-aspartate (NMDA)-induced depolarizations in rat cortical
789 slices or NMDA-induced cyclic GMP formation in immature rat cerebellum, nor did lamotrigine
790 displace compounds that are either competitive or noncompetitive ligands at this glutamate
791 receptor complex (CNQX, CGS, TCHP). The IC_{50} for lamotrigine effects on NMDA-induced
792 currents (in the presence of 3 μ M of glycine) in cultured hippocampal neurons exceeded
793 100 μ M.

794 **12.2 Pharmacodynamics**

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

803 Cardiovascular: In dogs, lamotrigine is extensively metabolized to a 2-N-methyl
804 metabolite. This metabolite causes dose-dependent prolongation of the PR interval, widening of
805 the QRS complex, and, at higher doses, complete AV conduction block. Similar cardiovascular
806 effects are not anticipated in humans because only trace amounts of the 2-N-methyl metabolite
807 (<0.6% of lamotrigine dose) have been found in human urine [see *Clinical Pharmacology*
808 *(12.3)*]. However, it is conceivable that plasma concentrations of this metabolite could be
809 increased in patients with a reduced capacity to glucuronidate lamotrigine (e.g., in patients with
810 liver disease, patients taking concomitant medications that inhibit glucuronidation).

811 **12.3 Pharmacokinetics**

812 In comparison with immediate-release lamotrigine, the plasma lamotrigine levels
813 following administration of LAMICTAL XR are not associated with any significant changes in
814 trough plasma concentrations, and are characterized by lower peaks, longer time to peaks, and
815 lower peak-to-trough fluctuation, as described in detail below.

816 Absorption: Lamotrigine is absorbed after oral administration with negligible first-pass
817 metabolism. The bioavailability of lamotrigine is not affected by food.

818 In an open-label, crossover study of 44 subjects with epilepsy receiving concomitant
819 AEDs, the steady-state pharmacokinetics of lamotrigine were compared following administration
820 of equivalent total doses of LAMICTAL XR given once daily with those of lamotrigine
821 immediate-release given twice daily. In this study, the median time to peak concentration (T_{max})
822 following administration of LAMICTAL XR was 4 to 6 hours in subjects taking carbamazepine,
823 phenytoin, phenobarbital, or primidone; 9 to 11 hours in subjects taking valproate; and 6 to
824 10 hours in subjects taking AEDs other than carbamazepine, phenytoin, phenobarbital,
825 primidone, or valproate. In comparison, the median T_{max} following administration of immediate-
826 release lamotrigine was between 1 and 1.5 hours.

827 The steady-state trough concentrations for extended-release lamotrigine were similar to
828 or higher than those of immediate-release lamotrigine depending on concomitant AED (Table 6).
829 A mean reduction in the lamotrigine C_{max} by 11% to 29% was observed for LAMICTAL XR
830 compared with immediate-release lamotrigine, resulting in a decrease in the peak-to-trough
831 fluctuation in serum lamotrigine concentrations. However, in some subjects receiving enzyme-
832 inducing AEDs, a reduction in C_{max} of 44% to 77% was observed. The degree of fluctuation was
833 reduced by 17% in subjects taking enzyme-inducing AEDs; 34% in subjects taking valproate;
834 and 37% in subjects taking AEDs other than carbamazepine, phenytoin, phenobarbital,
835 primidone, or valproate. LAMICTAL XR and immediate-release lamotrigine regimens were
836 similar with respect to area under the curve (AUC, a measure of the extent of bioavailability) for
837 subjects receiving AEDs other than those known to induce the metabolism of lamotrigine. The
838 relative bioavailability of extended-release lamotrigine was approximately 21% lower than
839 immediate-release lamotrigine in subjects receiving enzyme-inducing AEDs. However, a
840 reduction in exposure of up to 70% was observed in some subjects in this group when they
841 switched to LAMICTAL XR. Therefore, doses may need to be adjusted in some patients based
842 on therapeutic response.

843

844 **Table 6. Steady-State Bioavailability of LAMICTAL XR Relative to Immediate-Release**
845 **Lamotrigine at Equivalent Daily Doses (Ratio of Extended-Release to Immediate-Release**
846 **90% CI)**

Concomitant Antiepileptic Drug	AUC _(0-24ss)	C _{max}	C _{min}
Enzyme-inducing antiepileptic drugs ^a	0.79 (0.69, 0.90)	0.71 (0.61, 0.82)	0.99 (0.89, 1.09)
Valproate	0.94 (0.81, 1.08)	0.88 (0.75, 1.03)	0.99 (0.88, 1.10)
Antiepileptic drugs other than enzyme-inducing antiepileptic drugs ^a or valproate	1.00 (0.88, 1.14)	0.89 (0.78, 1.03)	1.14 (1.03, 1.25)

847 ^a Enzyme-inducing antiepileptic drugs include carbamazepine, phenytoin, phenobarbital, and
848 primidone.

849

850 **Dose Proportionality:** In healthy volunteers not receiving any other medications and
851 given LAMICTAL XR once daily, the systemic exposure to lamotrigine increased in direct
852 proportion to the dose administered over the range of 50 to 200 mg. At doses between 25 and
853 50 mg, the increase was less than dose proportional, with a 2-fold increase in dose resulting in an
854 approximately 1.6-fold increase in systemic exposure.

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

NDA 022115/S-004 & S-014
FDA Proposed Labeling Text dated 12/23/2014
Page 28

NDA 022115/S-004 & S-014
FDA Proposed Labeling Text dated 12/23/2014
Page 29

892 **Table 7. Mean Pharmacokinetic Parameters^a of Immediate-Release Lamotrigine in**
893 **Healthy Volunteers and Adult Subjects With Epilepsy**

Adult Study Population	Number of Subjects	t_{1/2}: Elimination Half-life (h)	CL/F: Apparent Plasma Clearance (mL/min/kg)
Healthy volunteers taking no other medications:			
Single-dose lamotrigine	179	32.8 (14.0-103.0)	0.44 (0.12-1.10)
Multiple-dose lamotrigine	36	25.4 (11.6-61.6)	0.58 (0.24-1.15)
Healthy volunteers taking valproate:			
Single-dose lamotrigine	6	48.3 (31.5-88.6)	0.30 (0.14-0.42)
Multiple-dose lamotrigine	18	70.3 (41.9-113.5)	0.18 (0.12-0.33)
Subjects with epilepsy taking valproate only:			
Single-dose lamotrigine	4	58.8 (30.5-88.8)	0.28 (0.16-0.40)
Subjects with epilepsy taking carbamazepine, phenytoin, phenobarbital, or primidone^b plus valproate:			
Single-dose lamotrigine	25	27.2 (11.2-51.6)	0.53 (0.27-1.04)
Subjects with epilepsy taking carbamazepine, phenytoin, phenobarbital, or primidone:^b			
Single-dose lamotrigine	24	14.4 (6.4-30.4)	1.10 (0.51-2.22)
Multiple-dose lamotrigine	17	12.6 (7.5-23.1)	1.21 (0.66-1.82)

894 ^a The majority of parameter means determined in each study had coefficients of variation
895 between 20% and 40% for half-life and CL/F and between 30% and 70% for T_{max}. The
896 overall mean values were calculated from individual study means that were weighted based
897 on the number of volunteers/subjects in each study. The numbers in parentheses below each
898 parameter mean represent the range of individual volunteer/subject values across studies.

899 ^b Carbamazepine, phenytoin, phenobarbital, and primidone have been shown to increase the
900 apparent clearance of lamotrigine. Estrogen-containing oral contraceptives and other drugs,
901 such as rifampin and protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir, that
902 induce lamotrigine glucuronidation have also been shown to increase the apparent clearance
903 of lamotrigine [*see Drug Interactions (7)*].
904

905 **Drug Interactions:** The apparent clearance of lamotrigine is affected by the
906 coadministration of certain medications [*see Warnings and Precautions (5.7, 5.11), Drug*
907 *Interactions (7)*].

908 The net effects of drug interactions with lamotrigine, based on drug interaction studies
909 using immediate-release lamotrigine, are summarized in Tables 5 and 8, followed by details of
910 the drug interaction studies below.
911

912 **Table 8. Summary of Drug Interactions With Lamotrigine**

Drug	Drug Plasma Concentration With Adjunctive Lamotrigine ^a	Lamotrigine Plasma Concentration With Adjunctive Drugs ^b
Oral contraceptives (e.g., ethinylestradiol/levonorgestrel) ^c	↔ ^d	↓
Atazanavir/ritonavir	↔ ^e	↓
Bupropion	Not assessed	↔
Carbamazepine	↔	↓
Carbamazepine epoxide ^f	?	
Felbamate	Not assessed	↔
Gabapentin	Not assessed	↔
Levetiracetam	↔	↔
Lithium	↔	Not assessed
Lopinavir/ritonavir	↔ ^e	↓
Olanzapine	↔	↔ ^g
Oxcarbazepine	↔	↔
10-Monohydroxy oxcarbazepine metabolite ^h	↔	
Phenobarbital/primidone	↔	↓
Phenytoin	↔	↓
Pregabalin	↔	↔
Rifampin	Not assessed	↓
Risperidone	↔	Not assessed
9-hydroxyrisperidone ⁱ	↔	
Topiramate	↔ ^j	↔
Valproate	↓	↑

Valproate + phenytoin and/or carbamazepine	Not assessed	↔
Zonisamide	Not assessed	↔

- 913 ^a From adjunctive clinical trials and volunteer trials.
- 914 ^b Net effects were estimated by comparing the mean clearance values obtained in adjunctive
915 clinical trials and volunteer trials.
- 916 ^c The effect of other hormonal contraceptive preparations or hormone replacement therapy on
917 the pharmacokinetics of lamotrigine has not been systematically evaluated in clinical trials,
918 although the effect may be similar to that seen with the ethinylestradiol/levonorgestrel
919 combinations.
- 920 ^d Modest decrease in levonorgestrel.
- 921 ^e Compared to historical controls.
- 922 ^f Not administered, but an active metabolite of carbamazepine.
- 923 ^g Slight decrease, not expected to be clinically relevant.
- 924 ^h Not administered, but an active metabolite of oxcarbazepine.
- 925 ⁱ Not administered, but an active metabolite of risperidone.
- 926 ^j Slight increase, not expected to be clinically relevant.
- 927 ↔ = No significant effect.
- 928 ? = Conflicting data.
- 929

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

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

945 In the same study, coadministration of lamotrigine (300 mg/day) in 16 female volunteers
946 did not affect the pharmacokinetics of the ethinylestradiol component of the oral contraceptive
947 preparation. There were mean decreases in the AUC and C_{max} of the levonorgestrel component of
948 19% and 12%, respectively. Measurement of serum progesterone indicated that there was no
949 hormonal evidence of ovulation in any of the 16 volunteers, although measurement of serum

950 FSH, LH, and estradiol indicated that there was some loss of suppression of the hypothalamic-
951 pituitary-ovarian axis.

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

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

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

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

966 Atazanavir/Ritonavir: In a study in healthy volunteers, daily doses of
967 atazanavir/ritonavir (300 mg/100 mg) reduced the plasma AUC and C_{max} of lamotrigine (single
968 100-mg dose) by an average of 32% and 6%, respectively, and shortened the elimination half-
969 lives by 27%. In the presence of atazanavir/ritonavir (300 mg/100 mg), the metabolite-to-
970 lamotrigine ratio was increased from 0.45 to 0.71 consistent with induction of glucuronidation.
971 The pharmacokinetics of atazanavir/ritonavir were similar in the presence of concomitant
972 lamotrigine to the historical data of the pharmacokinetics in the absence of lamotrigine.

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

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

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

986 Esomeprazole: In a study of 30 subjects, coadministration of LAMICTAL XR with
987 esomeprazole resulted in no significant change in lamotrigine levels and a small decrease in T_{max} .
988 The levels of gastric pH were not altered compared with pre-lamotrigine dosing.

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

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

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

997 Levetiracetam: Potential drug interactions between levetiracetam and lamotrigine were
998 assessed by evaluating serum concentrations of both agents during placebo-controlled clinical
999 trials. These data indicate that lamotrigine does not influence the pharmacokinetics of
1000 levetiracetam and that levetiracetam does not influence the pharmacokinetics of lamotrigine.

1001 Lithium: The pharmacokinetics of lithium were not altered in healthy subjects (n = 20) by
1002 coadministration of lamotrigine (100 mg/day) for 6 days.

1003 Lopinavir/Ritonavir: The addition of lopinavir (400 mg twice daily)/ritonavir (100 mg
1004 twice daily) decreased the AUC, C_{max}, and elimination half-life of lamotrigine by approximately
1005 50% to 55.4% in 18 healthy subjects. The pharmacokinetics of lopinavir/ritonavir were similar
1006 with concomitant lamotrigine, compared to that in historical controls.

1007 Olanzapine: The AUC and C_{max} of olanzapine were similar following the addition of
1008 olanzapine (15 mg once daily) to lamotrigine (200 mg once daily) in healthy male volunteers
1009 (n = 16) compared with the AUC and C_{max} in healthy male volunteers receiving olanzapine alone
1010 (n = 16).

1011 In the same trial, the AUC and C_{max} of lamotrigine were reduced on average by 24% and
1012 20%, respectively, following the addition of olanzapine to lamotrigine in healthy male volunteers
1013 compared with those receiving lamotrigine alone. This reduction in lamotrigine plasma
1014 concentrations is not expected to be clinically relevant.

1015 Oxcarbazepine: The AUC and C_{max} of oxcarbazepine and its active 10-monohydroxy
1016 oxcarbazepine metabolite were not significantly different following the addition of
1017 oxcarbazepine (600 mg twice daily) to lamotrigine (200 mg once daily) in healthy male
1018 volunteers (n = 13) compared with healthy male volunteers receiving oxcarbazepine alone
1019 (n = 13).

1020 In the same trial, the AUC and C_{max} of lamotrigine were similar following the addition of
1021 oxcarbazepine (600 mg twice daily) to lamotrigine in healthy male volunteers compared with
1022 those receiving lamotrigine alone. Limited clinical data suggest a higher incidence of headache,
1023 dizziness, nausea, and somnolence with coadministration of lamotrigine and oxcarbazepine
1024 compared with lamotrigine alone or oxcarbazepine alone.

1025 Phenobarbital, Primidone: The addition of phenobarbital or primidone decreases
1026 lamotrigine steady-state concentrations by approximately 40%.

1027 Phenytoin: Lamotrigine has no appreciable effect on steady-state phenytoin plasma
1028 concentrations in patients with epilepsy. The addition of phenytoin decreases lamotrigine steady-
1029 state concentrations by approximately 40%.

1030 Pregabalin: Steady-state trough plasma concentrations of lamotrigine were not affected
1031 by concomitant pregabalin (200 mg 3 times daily) administration. There are no pharmacokinetic
1032 interactions between lamotrigine and pregabalin.

1033 Rifampin: In 10 male volunteers, rifampin (600 mg/day for 5 days) significantly
1034 increased the apparent clearance of a single 25-mg dose of lamotrigine by approximately 2-fold
1035 (AUC decreased by approximately 40%).

1036 Risperidone: In a 14 healthy volunteers study, multiple oral doses of lamotrigine 400 mg
1037 daily had no clinically significant effect on the single-dose pharmacokinetics of risperidone 2 mg
1038 and its active metabolite 9-OH risperidone. Following the coadministration of risperidone 2 mg
1039 with lamotrigine, 12 of the 14 volunteers reported somnolence compared with 1 out of 20 when
1040 risperidone was given alone, and none when lamotrigine was administered alone.

1041 Topiramate: Topiramate resulted in no change in plasma concentrations of lamotrigine.
1042 Administration of lamotrigine resulted in a 15% increase in topiramate concentrations.

1043 Valproate: When lamotrigine was administered to healthy volunteers (n = 18) receiving
1044 valproate, the trough steady-state valproate plasma concentrations decreased by an average of
1045 25% over a 3-week period, and then stabilized. However, adding lamotrigine to the existing
1046 therapy did not cause a change in valproate plasma concentrations in either adult or pediatric
1047 patients in controlled clinical trials.

1048 The addition of valproate increased lamotrigine steady-state concentrations in normal
1049 volunteers by slightly more than 2-fold. In 1 trial, maximal inhibition of lamotrigine clearance
1050 was reached at valproate doses between 250 and 500 mg/day and did not increase as the
1051 valproate dose was further increased.

1052 Zonisamide: In a study in 18 patients with epilepsy, coadministration of zonisamide
1053 (200 to 400 mg/day) with lamotrigine (150 to 500 mg/day for 35 days) had no significant effect
1054 on the pharmacokinetics of lamotrigine.

1055 Known Inducers or Inhibitors of Glucuronidation: Drugs other than those listed above
1056 have not been systematically evaluated in combination with lamotrigine. Since lamotrigine is
1057 metabolized predominately by glucuronic acid conjugation, drugs that are known to induce or
1058 inhibit glucuronidation may affect the apparent clearance of lamotrigine, and doses of
1059 LAMICTAL XR may require adjustment based on clinical response.

1060 Other: Results of in vitro experiments suggest that clearance of lamotrigine is unlikely to
1061 be reduced by concomitant administration of amitriptyline, clonazepam, clozapine, fluoxetine,
1062 haloperidol, lorazepam, phenelzine, sertraline, or trazodone.

1063 Results of in vitro experiments suggest that lamotrigine does not reduce the clearance of
1064 drugs eliminated predominantly by CYP2D6.

1065 Specific Populations: Subjects With Renal Impairment: Twelve volunteers with
1066 chronic renal failure (mean creatinine clearance: 13 mL/min, range: 6 to 23) and another 6

1067 individuals undergoing hemodialysis were each given a single 100-mg dose of immediate-release
1068 lamotrigine. The mean plasma half-lives determined in the study were 42.9 hours (chronic renal
1069 failure), 13.0 hours (during hemodialysis), and 57.4 hours (between hemodialysis) compared
1070 with 26.2 hours in healthy volunteers. On average, approximately 20% (range: 5.6 to 35.1) of the
1071 amount of lamotrigine present in the body was eliminated by hemodialysis during a 4-hour
1072 session [see *Dosage and Administration (2.1)*].

1073 **Hepatic Disease:** The pharmacokinetics of lamotrigine following a single 100-mg
1074 dose of immediate-release lamotrigine were evaluated in 24 subjects with mild, moderate, and
1075 severe hepatic impairment (Child-Pugh Classification system) and compared with 12 subjects
1076 without hepatic impairment. The subjects with severe hepatic impairment were without ascites
1077 (n = 2) or with ascites (n = 5). The mean apparent clearances of lamotrigine in subjects with mild
1078 (n = 12), moderate (n = 5), severe without ascites (n = 2), and severe with ascites (n = 5) liver
1079 impairment were 0.30 ± 0.09 , 0.24 ± 0.1 , 0.21 ± 0.04 , and 0.15 ± 0.09 mL/min/kg, respectively,
1080 as compared with 0.37 ± 0.1 mL/min/kg in the healthy controls. Mean half-lives of lamotrigine
1081 in subjects with mild, moderate, severe without ascites, and severe with ascites hepatic
1082 impairment were 46 ± 20 , 72 ± 44 , 67 ± 11 , and 100 ± 48 hours, respectively, as compared with
1083 33 ± 7 hours in healthy controls [see *Dosage and Administration (2.1)*].

1084 **Elderly:** The pharmacokinetics of lamotrigine following a single 150-mg dose of
1085 immediate-release lamotrigine were evaluated in 12 elderly volunteers between the ages of 65
1086 and 76 years (mean creatinine clearance: 61 mL/min, range: 33 to 108 mL/min). The mean
1087 half-life of lamotrigine in these subjects was 31.2 hours (range: 24.5 to 43.4 hours), and the mean
1088 clearance was 0.40 mL/min/kg (range: 0.26 to 0.48 mL/min/kg).

1089 **Gender:** The clearance of lamotrigine is not affected by gender. However, during
1090 dose escalation of immediate-release lamotrigine in 1 clinical trial in patients with epilepsy on a
1091 stable dose of valproate (n = 77), mean trough lamotrigine concentrations unadjusted for weight
1092 were 24% to 45% higher (0.3 to 1.7 mcg/mL) in females than in males.

1093 **Race:** The apparent oral clearance of lamotrigine was 25% lower in non-Caucasians
1094 than Caucasians.

1095 **Pediatric Patients:** Safety and effectiveness of LAMICTAL XR for use in patients
1096 younger than 13 years have not been established.

1097 **13 NONCLINICAL TOXICOLOGY**

1098 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

1099 No evidence of carcinogenicity was seen in mouse or rat following oral administration of
1100 lamotrigine for up to 2 years at doses up to 30 mg/kg/day and 10 to 15 mg/kg/day in mouse and
1101 rat, respectively. The highest doses tested are less than the human dose of 400 mg/day on a body
1102 surface area (mg/m²) basis.

1103 Lamotrigine was negative in in vitro gene mutation (Ames and mouse lymphoma *tk*)
1104 assays and in clastogenicity (in vitro human lymphocyte and in vivo rat bone marrow) assays.

1105 No evidence of impaired fertility was detected in rats given oral doses of lamotrigine up
1106 to 20 mg/kg/day. The highest dose tested is less than the human dose of 400 mg/day on a mg/m²
1107 basis.

1108 **14 CLINICAL STUDIES**

1109 **14.1 Adjunctive Therapy for Primary Generalized Tonic-Clonic Seizures**

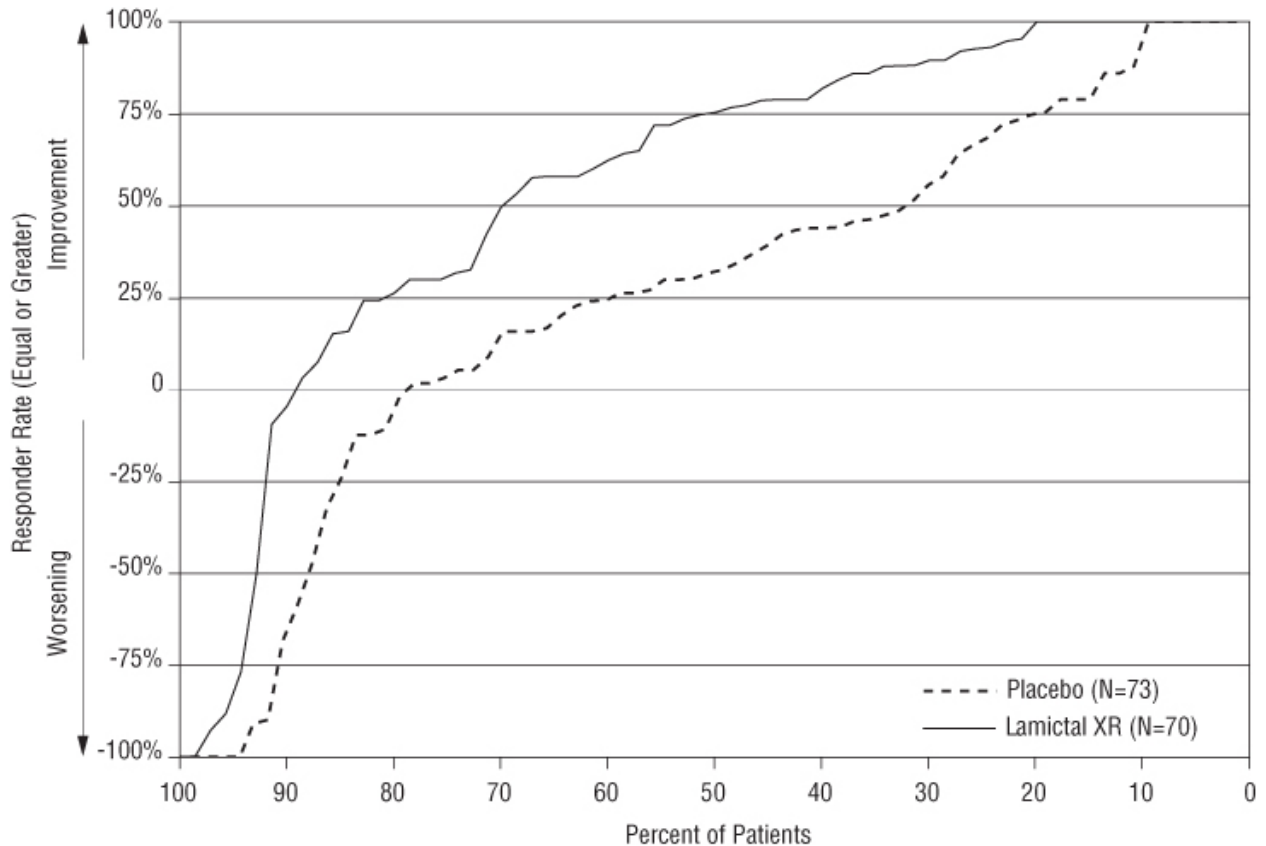
1110 The effectiveness of LAMICTAL XR as adjunctive therapy in subjects with PGTC
1111 seizures was established in a 19-week, international, multicenter, double-blind, randomized,
1112 placebo-controlled trial in 143 patients aged 13 years and older (n = 70 on LAMICTAL XR, n =
1113 73 on placebo). Patients with at least 3 PGTC seizures during an 8-week baseline phase were
1114 randomized to 19 weeks of treatment with LAMICTAL XR or placebo added to their current
1115 AED regimen of up to 2 drugs. Patients were dosed on a fixed-dose regimen, with target doses
1116 ranging from 200 to 500 mg/day of LAMICTAL XR based on concomitant AEDs (target dose =
1117 200 mg for valproate, 300 mg for AEDs not altering plasma lamotrigine levels, and 500 mg for
1118 enzyme-inducing AEDs).

1119 The primary efficacy endpoint was percent change from baseline in PGTC seizure
1120 frequency during the double-blind treatment phase. For the intent-to-treat population, the median
1121 percent reduction in PGTC seizure frequency was 75% in patients treated with LAMICTAL XR
1122 and 32% in patients treated with placebo, a difference that was statistically significant, defined as
1123 a 2-sided *P* value ≤ 0.05 .

1124 Figure 1 presents the percentage of patients (X-axis) with a percent reduction in PGTC
1125 seizure frequency (responder rate) from baseline through the entire treatment period at least as
1126 great as that represented on the Y-axis. A positive value on the Y-axis indicates an improvement
1127 from baseline (i.e., a decrease in seizure frequency), while a negative value indicates a worsening
1128 from baseline (i.e., an increase in seizure frequency). Thus, in a display of this type, a curve for
1129 an effective treatment is shifted to the left of the curve for placebo. The proportion of patients
1130 achieving any particular level of reduction in PGTC seizure frequency was consistently higher
1131 for the group treated with LAMICTAL XR compared with the placebo group. For example, 70%
1132 of patients randomized to LAMICTAL XR experienced a 50% or greater reduction in PGTC
1133 seizure frequency, compared with 32% of patients randomized to placebo. Patients with an
1134 increase in seizure frequency >100% are represented on the Y-axis as equal to or greater than
1135 -100%.
1136

NDA 022115/S-004 & S-014
FDA Proposed Labeling Text dated 12/23/2014
Page 37

1137 **Figure 1. Proportion of Patients by Responder Rate for LAMICTAL XR and Placebo**
1138 **Group (Primary Generalized Tonic-Clonic Seizures Study)**



1139

1140 14.2 Adjunctive Therapy for Partial-Onset Seizures

1141 The effectiveness of immediate-release lamotrigine as adjunctive therapy was initially
1142 established in 3 pivotal, multicenter, placebo-controlled, double-blind clinical trials in 355 adults
1143 with refractory partial-onset seizures.

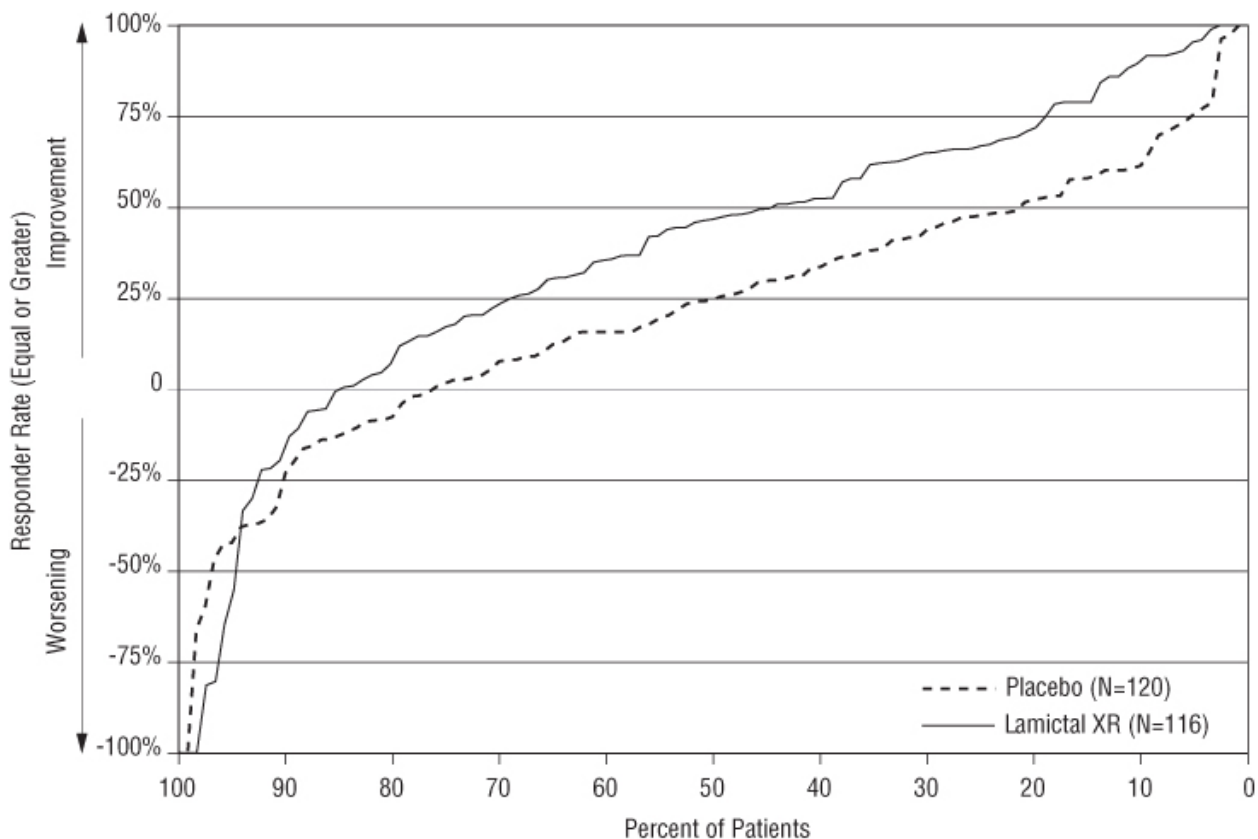
1144 The effectiveness of LAMICTAL XR as adjunctive therapy in partial-onset seizures, with
1145 or without secondary generalization, was established in a 19-week, multicenter, double-blind,
1146 placebo-controlled trial in 236 patients aged 13 years and older (approximately 93% of patients
1147 were aged 16 to 65 years). Approximately 36% were from the U.S. and approximately 64% were
1148 from other countries including Argentina, Brazil, Chile, Germany, India, Korea, Russian
1149 Federation, and Ukraine. Patients with at least 8 partial-onset seizures during an 8-week
1150 prospective baseline phase (or 4-week prospective baseline coupled with a 4-week historical
1151 baseline documented with seizure diary data) were randomized to treatment with
1152 LAMICTAL XR (n = 116) or placebo (n = 120) added to their current regimen of 1 or 2 AEDs.
1153 Approximately half of the patients were taking 2 concomitant AEDs at baseline. Target doses
1154 ranged from 200 to 500 mg/day of LAMICTAL XR based on concomitant AED (target dose =
1155 200 mg for valproate, 300 mg for AEDs not altering plasma lamotrigine, and 500 mg for
1156 enzyme-inducing AEDs). The median partial seizure frequency per week at baseline was 2.3 for
1157 LAMICTAL XR and 2.1 for placebo.

1158 The primary endpoint was the median percent change from baseline in partial-onset
1159 seizure frequency during the entire double-blind treatment phase. The median percent reductions
1160 in weekly partial-onset seizures were 47% in patients treated with LAMICTAL XR and 25% on
1161 placebo, a difference that was statistically significant, defined as a 2-sided P value ≤ 0.05 .

1162 Figure 2 presents the percentage of patients (X-axis) with a percent reduction in partial-
1163 onset seizure frequency (responder rate) from baseline through the entire treatment period at
1164 least as great as that represented on the Y-axis. The proportion of patients achieving any
1165 particular level of reduction in partial-onset seizure frequency was consistently higher for the
1166 group treated with LAMICTAL XR compared with the placebo group. For example, 44% of
1167 patients randomized to LAMICTAL XR experienced a 50% or greater reduction in partial-onset
1168 seizure frequency compared with 21% of patients randomized to placebo.

1169

1170 **Figure 2. Proportion of Patients by Responder Rate for LAMICTAL XR and Placebo**
1171 **Group (Partial-Onset Seizure Study)**



1172

1173

1174 14.3 Conversion to Monotherapy for Partial-Onset Seizures

1175 The effectiveness of LAMICTAL XR as monotherapy for partial-onset seizures was
1176 established in a historical control trial in 223 adults with partial-onset seizures. The historical
1177 control methodology is described in a publication by French, et al. [see References (15)]. Briefly,
1178 in this study, patients were randomized to ultimately receive either LAMICTAL XR 300 or

1179 250 mg once a day, and their responses were compared with those of a historical control group.
1180 The historical control consisted of a pooled analysis of the control groups from 8 studies of
1181 similar design, which utilized a subtherapeutic dose of an AED as a comparator. Statistical
1182 superiority to the historical control was considered to be demonstrated if the upper 95%
1183 confidence interval for the proportion of patients meeting escape criteria in patients receiving
1184 LAMICTAL XR remained below the lower 95% prediction interval of 65.3% derived from the
1185 historical control data.

1186 In this study, patients aged 13 years and older experienced at least 4 partial-onset seizures
1187 during an 8-week baseline period with at least 2 seizures occurring during each of 2 consecutive
1188 4-week periods while receiving valproate or a non-enzyme-inducing AED. LAMICTAL XR was
1189 added to either valproate or a non-enzyme-inducing AED over a 6- to 7-week period followed
1190 by the gradual withdrawal of the background AED. Patients were then continued on
1191 monotherapy with LAMICTAL XR for 12 weeks. The escape criteria were 1 or more of the
1192 following: (1) doubling of average monthly seizure count during any 28 consecutive days,
1193 (2) doubling of highest consecutive 2-day seizure frequency during the entire treatment phase,
1194 (3) emergence of a new seizure type compared with baseline (4) clinically significant
1195 prolongation of generalized tonic-clonic seizures or worsening of seizure considered by the
1196 investigator to require intervention. These criteria were similar to those in the 8 controlled trials
1197 from which the historical control group was constituted.

1198 The upper 95% confidence limits of the proportion of subjects meeting escape criteria
1199 (40.2% at 300 mg/day and 44.5% at 250 mg/day) were below the threshold of 65.3% derived
1200 from the historical control data.

1201 Although the study population was not fully comparable with the historical controlled
1202 population and the study was not fully blinded, numerous sensitivity analyses supported the
1203 primary results. Efficacy was further supported by the established effectiveness of the
1204 immediate-release formulation as monotherapy.

1205 **15 REFERENCES**

1206 1. French JA, Wang S, Warnock B, Temkin N. Historical control monotherapy design in the
1207 treatment of epilepsy. *Epilepsia*. 2010; 51(10):1936-1943.

1208 **16 HOW SUPPLIED/STORAGE AND HANDLING**

1209 **LAMICTAL XR (lamotrigine) Extended-Release Tablets**

1210 25 mg, yellow with a white center, round, biconvex, film-coated tablets printed on one
1211 face in black ink with “LAMICTAL” and “XR 25”, unit-of-use bottles of 30 with orange caps
1212 (NDC 0173-0754-00).

1213 50 mg, green with a white center, round, biconvex, film-coated tablets printed on one
1214 face in black ink with “LAMICTAL” and “XR 50”, unit-of-use bottles of 30 with orange caps
1215 (NDC 0173-0755-00).

1216 100 mg, orange with a white center, round, biconvex, film-coated tablets printed on one
1217 face in black ink with “LAMICTAL” and “XR 100”, unit-of-use bottles of 30 with orange caps
1218 (NDC 0173-0756-00).

1219 200 mg, blue with a white center, round, biconvex, film-coated tablets printed on one
1220 face in black ink with “LAMICTAL” and “XR 200”, unit-of-use bottles of 30 with orange caps
1221 (NDC 0173-0757-00).

1222 250 mg, purple with a white center, caplet-shaped, film-coated tablets printed on one face
1223 in black ink with “LAMICTAL” and “XR 250”, unit-of-use bottles of 30 with orange caps (NDC
1224 0173-0781-00).

1225 300 mg, gray with a white center, caplet-shaped, film-coated tablets printed on one face
1226 in black ink with “LAMICTAL” and “XR 300”, unit-of-use bottles of 30 with orange caps (NDC
1227 0173-0761-00).

1228 **LAMICTAL XR (lamotrigine) Patient Titration Kit for Patients Taking Valproate**
1229 **(Blue XR Kit)**

1230 25 mg, yellow with a white center, round, biconvex, film-coated tablets printed on one
1231 face in black ink with “LAMICTAL” and “XR 25” and 50 mg, green with a white center, round,
1232 biconvex, film-coated tablets printed on one face in black ink with “LAMICTAL” and “XR 50”;
1233 blisterpack of 21/25-mg tablets and 7/50-mg tablets (NDC 0173-0758-00).

1234 **LAMICTAL XR (lamotrigine) Patient Titration Kit for Patients Taking**
1235 **Carbamazepine, Phenytoin, Phenobarbital, or Primidone, and Not Taking Valproate**
1236 **(Green XR Kit)**

1237 50 mg, green with a white center, round, biconvex, film-coated tablets printed on one
1238 face in black ink with “LAMICTAL” and “XR 50”; 100 mg, orange with a white center, round,
1239 biconvex, film-coated tablets printed on one face in black ink with “LAMICTAL” and “XR
1240 100”; and 200 mg, blue with a white center, round, biconvex, film-coated tablets printed on one
1241 face in black ink with “LAMICTAL” and “XR 200”; blisterpack of 14/50-mg tablets, 14/100-mg
1242 tablets, and 7/200-mg tablets (NDC 0173-0759-00).

1243 **LAMICTAL XR (lamotrigine) Patient Titration Kit for Patients Not Taking**
1244 **Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate (Orange XR Kit)**

1245 25 mg, yellow with a white center, round, biconvex, film-coated tablets printed on one
1246 face in black ink with “LAMICTAL” and “XR 25”; 50 mg, green with a white center, round,
1247 biconvex, film-coated tablets printed on one face in black ink with “LAMICTAL” and “XR 50”;
1248 and 100 mg, orange with a white center, round, biconvex, film-coated tablets printed on one face
1249 in black ink with “LAMICTAL” and “XR 100”; blisterpack of 14/25-mg tablets, 14/50-mg
1250 tablets, and 7/100-mg tablets (NDC 0173-0760-00).

1251 **Storage:** Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see
1252 USP Controlled Room Temperature].

1253 **17 PATIENT COUNSELING INFORMATION**

1254 Advise the patient to read the FDA-approved patient labeling (Medication Guide).

1255 Rash: Prior to initiation of treatment with LAMICTAL XR, inform patients that a rash or
1256 other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy) may herald a serious
1257 medical event and instruct them to report any such occurrence to their physician immediately.

1258 Multiorgan Hypersensitivity Reactions, Blood Dyscrasias, and Organ Failure:
1259 Inform patients that multiorgan hypersensitivity reactions and acute multiorgan failure may
1260 occur with LAMICTAL. Isolated organ failure or isolated blood dyscrasias without evidence of
1261 multiorgan hypersensitivity may also occur. Instruct patients to contact their physician
1262 immediately if they experience any signs or symptoms of these conditions [*see Warnings and*
1263 *Precautions (5.2, 5.3)*].

1264 Suicidal Thinking and Behavior: Inform patients, their caregivers, and families that
1265 AEDs, including LAMICTAL XR, may increase the risk of suicidal thoughts and behavior.
1266 Instruct them to be alert for the emergence or worsening of symptoms of depression, any unusual
1267 changes in mood or behavior, or the emergence of suicidal thoughts or behavior or thoughts
1268 about self-harm. They should immediately report behaviors of concern to their physician.

1269 Worsening of Seizures: Advise patients to notify their physician if worsening of
1270 seizure control occurs.

1271 Central Nervous System Adverse Effects: Inform patients that LAMICTAL XR may
1272 cause dizziness, somnolence, and other symptoms and signs of central nervous system
1273 depression. Accordingly, instruct them neither to drive a car nor to operate other complex
1274 machinery until they have gained sufficient experience on LAMICTAL XR to gauge whether or
1275 not it adversely affects their mental and/or motor performance.

1276 Pregnancy and Nursing: Instruct patients to notify their physician if they become
1277 pregnant or intend to become pregnant during therapy and if they intend to breastfeed or are
1278 breastfeeding an infant.

1279 Encourage patients to enroll in the NAAED Pregnancy Registry if they become pregnant.
1280 This registry is collecting information about the safety of antiepileptic drugs during pregnancy.
1281 To enroll, patients can call the toll-free number 1-888-233-2334 [*see Use in Specific Populations*
1282 *(8.1)*].

1283 Inform patients who intend to breastfeed that LAMICTAL XR is present in breast milk
1284 and advise them to monitor their child for potential adverse effects of this drug. Discuss the
1285 benefits and risks of continuing breastfeeding.

1286 Oral Contraceptive Use: Instruct women to notify their physician if they plan to start or
1287 stop use of oral contraceptives or other female hormonal preparations. Starting estrogen-
1288 containing oral contraceptives may significantly decrease lamotrigine plasma levels and stopping
1289 estrogen-containing oral contraceptives (including the pill-free week) may significantly increase
1290 lamotrigine plasma levels [*see Warnings and Precautions (5.7), Clinical Pharmacology (12.3)*].
1291 Also instruct women to promptly notify their physician if they experience adverse reactions or
1292 changes in menstrual pattern (e.g., break-through bleeding) while receiving LAMICTAL XR in
1293 combination with these medications.

1294 Discontinuing LAMICTAL XR: Instruct patients to notify their physician if they stop
1295 taking LAMICTAL XR for any reason and not to resume LAMICTAL XR without consulting
1296 their physician.

1297 Aseptic Meningitis: Inform patients that LAMICTAL XR may cause aseptic meningitis.
1298 Instruct them to notify their physician immediately if they develop signs and symptoms of
1299 meningitis such as headache, fever, nausea, vomiting, stiff neck, rash, abnormal sensitivity to
1300 light, myalgia, chills, confusion, or drowsiness while taking LAMICTAL XR.

1301 Potential Medication Errors: Medication errors involving LAMICTAL have occurred.
1302 In particular the names LAMICTAL or lamotrigine can be confused with the names of other
1303 commonly used medications. Medication errors may also occur between the different
1304 formulations of LAMICTAL. To reduce the potential of medication errors, write and say
1305 LAMICTAL XR clearly. Depictions of the LAMICTAL XR Extended-Release Tablets can be
1306 found in the Medication Guide. Each LAMICTAL XR tablet has a distinct color and white
1307 center, and is printed with “LAMICTAL XR” and the tablet strength. These distinctive features
1308 serve to identify the different presentations of the drug and thus may help reduce the risk of
1309 medication errors. LAMICTAL XR is supplied in round, unit-of-use bottles with orange caps
1310 containing 30 tablets. The label on the bottle includes a depiction of the tablets that further
1311 communicates to patients and pharmacists that the medication is LAMICTAL XR and the
1312 specific tablet strength included in the bottle. The unit-of-use bottle with a distinctive orange cap
1313 and distinctive bottle label features serves to identify the different presentations of the drug and
1314 thus may help to reduce the risk of medication errors. **To avoid a medication error of using the**
1315 **wrong drug or formulation, strongly advise patients to visually inspect their tablets to**
1316 **verify that they are LAMICTAL XR each time they fill their prescription and to**
1317 **immediately talk to their doctor/pharmacist if they receive a LAMICTAL XR tablet**
1318 **without a white center and without “LAMICTAL XR” and the strength printed on the**
1319 **tablet as they may have received the wrong medication** [*see Dosage Forms and Strengths (3),*
1320 *How Supplied/Storage and Handling (16)].*

1321

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1331 LXR:xPI

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1334

MEDICATION GUIDE

1335

1336 **LAMICTAL® (la-MIK-tal) XR™ (lamotrigine) Extended-Release Tablets**

1337

1338 Read this Medication Guide before you start taking LAMICTAL XR and each time you

1339 get a refill. There may be new information. This information does not take the place

1340 of talking with your healthcare provider about your medical condition or treatment.

1341 If you have questions about LAMICTAL XR, ask your healthcare provider or

1342 pharmacist.

1343

1344 **What is the most important information I should know about LAMICTAL**

1345 **XR?**

1346 **1. LAMICTAL XR may cause a serious skin rash that may cause you to be**

1347 **hospitalized or even cause death.**

1348 There is no way to tell if a mild rash will become more serious. A serious skin

1349 rash can happen at any time during your treatment with LAMICTAL XR, but is

1350 more likely to happen within the first 2 to 8 weeks of treatment. Children aged

1351 between 2 and 16 years have a higher chance of getting this serious skin rash

1352 while taking LAMICTAL XR. LAMICTAL XR is not approved for use in children

1353 younger than 13 years .

1354 The risk of getting a serious skin rash is higher if you:

1355 • take LAMICTAL XR while taking valproate [DEPAKENE® (valproic acid) or

1356 DEPAKOTE® (divalproex sodium)].

1357 • take a higher starting dose of LAMICTAL XR than your healthcare provider

1358 prescribed.

1359 • increase your dose of LAMICTAL XR faster than prescribed.

1360 **Call your healthcare provider right away if you have any of the**

1361 **following:**

1362 • **a skin rash**

1363 • **blistering or peeling of your skin**

1364 • **hives**

1365 • **painful sores in your mouth or around your eyes**

1366 These symptoms may be the first signs of a serious skin reaction. A healthcare

1367 provider should examine you to decide if you should continue taking LAMICTAL

1368 XR.

- 1369 **2. Other serious reactions, including serious blood problems or liver**
1370 **problems.** LAMICTAL XR can also cause other types of allergic reactions or
1371 serious problems that may affect organs and other parts of your body like your
1372 liver or blood cells. You may or may not have a rash with these types of
1373 reactions. Call your healthcare provider right away if you have any of these
1374 symptoms:
- 1375 • fever
 - 1376 • frequent infections
 - 1377 • severe muscle pain
 - 1378 • swelling of your face, eyes, lips, or tongue
 - 1379 • swollen lymph glands
 - 1380 • unusual bruising or bleeding
 - 1381 • weakness, fatigue
 - 1382 • yellowing of your skin or the white part of your eyes
- 1383 **3. Like other antiepileptic drugs, LAMICTAL XR may cause suicidal**
1384 **thoughts or actions in a very small number of people, about 1 in 500.**
- 1385 **Call a healthcare provider right away if you have any of these**
1386 **symptoms, especially if they are new, worse, or worry you:**
- 1387 • thoughts about suicide or dying
 - 1388 • attempt to commit suicide
 - 1389 • new or worse depression
 - 1390 • new or worse anxiety
 - 1391 • feeling agitated or restless
 - 1392 • panic attacks
 - 1393 • trouble sleeping (insomnia)
 - 1394 • new or worse irritability
 - 1395 • acting aggressive, being angry, or violent
 - 1396 • acting on dangerous impulses
 - 1397 • an extreme increase in activity and talking (mania)
 - 1398 • other unusual changes in behavior or mood
- 1399 **Do not stop LAMICTAL XR without first talking to a healthcare provider.**
- 1400 • Stopping LAMICTAL XR suddenly can cause serious problems.
 - 1401 • Suicidal thoughts or actions can be caused by things other than medicines. If
 - 1402 you have suicidal thoughts or actions, your healthcare provider may check
 - 1403 for other causes.
- 1404 **How can I watch for early symptoms of suicidal thoughts and actions?**
- 1405 • Pay attention to any changes, especially sudden changes, in mood,
 - 1406 behaviors, thoughts, or feelings.

- 1407 • Keep all follow-up visits with your healthcare provider as scheduled.
1408 • Call your healthcare provider between visits as needed, especially if you are
1409 worried about symptoms.

1410 **4. LAMICTAL XR may rarely cause aseptic meningitis, a serious**
1411 **inflammation of the protective membrane that covers the brain and**
1412 **spinal cord.**

1413 **Call your healthcare provider right away if you have any of the following**
1414 **symptoms:**

- 1415 • headache
1416 • fever
1417 • nausea
1418 • vomiting
1419 • stiff neck
1420 • rash
1421 • unusual sensitivity to light
1422 • muscle pains
1423 • chills
1424 • confusion
1425 • drowsiness

1426 Meningitis has many causes other than LAMICTAL XR, which your doctor would
1427 check for if you developed meningitis while taking LAMICTAL XR.

1428 **LAMICTAL XR can have other serious side effects.** For more information
1429 ask your healthcare provider or pharmacist. Tell your healthcare provider if you
1430 have any side effect that bothers you. Be sure to read the section below entitled
1431 “**What are the possible side effects of LAMICTAL XR?**”

1432 **5. Patients prescribed LAMICTAL have sometimes been given the wrong**
1433 **medicine because many medicines have names similar to LAMICTAL, so**
1434 **always check that you receive LAMICTAL XR.**

1435 Taking the wrong medication can cause serious health problems. When your
1436 healthcare provider gives you a prescription for LAMICTAL XR:







- 1437 • Make sure you can read it clearly.
1438 • Talk to your pharmacist to check that you are given the correct medicine.
1439 • Each time you fill your prescription, check the tablets you receive against the
1440 pictures of the tablets below.

1441 These pictures show the distinct wording, colors, and shapes of the tablets
1442 that help to identify the right strength of LAMICTAL XR. Immediately call your

1443 pharmacist if you receive a LAMICTAL XR tablet that does not look like one of
1444 the tablets shown below, as you may have received the wrong medication.

1445
1446

LAMICTAL XR (lamotrigine) Extended-Release Tablets

 25 mg, yellow with white center Imprinted with LAMICTAL XR 25	 50 mg, green with white center Imprinted with LAMICTAL XR 50	 100 mg, orange with white center Imprinted with LAMICTAL XR 100
 200 mg, blue with white center Imprinted with LAMICTAL XR 200	 250 mg, purple with white center Imprinted with LAMICTAL XR 250	 300 mg, gray with white center Imprinted with LAMICTAL XR 300

1447

1448 **What is LAMICTAL XR?**

1449 LAMICTAL XR is a prescription medicine used:

- 1450 • together with other medicines to treat primary generalized tonic-clonic seizures
1451 and partial onset seizures in people aged 13 years and older.
1452 • alone when changing from 1 other medicine used to treat partial-onset seizures
1453 in people aged 13 years and older.

1454 It is not known if LAMICTAL XR is safe or effective in children younger than 13
1455 years. Other forms of LAMICTAL can be used in children aged 2 to 12 years.

1456 It is not known if LAMICTAL XR is safe or effective when used alone as the first
1457 treatment of seizures.

1458

1459 **Who should not take LAMICTAL XR?**

1460 You should not take LAMICTAL XR if you have had an allergic reaction to
1461 lamotrigine or to any of the inactive ingredients in LAMICTAL XR. See the end of
1462 this leaflet for a complete list of ingredients in LAMICTAL XR.

1463

1464 **What should I tell my healthcare provider before taking LAMICTAL XR?**

- 1465 Before taking LAMICTAL XR, tell your healthcare provider about all of your medical
1466 conditions, including if you:
- 1467 • have had a rash or allergic reaction to another antiseizure medicine.
 - 1468 • have or have had depression, mood problems, or suicidal thoughts or behavior.
 - 1469 • have had aseptic meningitis after taking LAMICTAL (lamotrigine) or LAMICTAL
1470 XR.
 - 1471 • are taking oral contraceptives (birth control pills) or other female hormonal
1472 medicines. Do not start or stop taking birth control pills or other female
1473 hormonal medicine until you have talked with your healthcare provider. Tell your
1474 healthcare provider if you have any changes in your menstrual pattern such as
1475 breakthrough bleeding. Stopping these medicines may cause side effects (such
1476 as dizziness, lack of coordination, or double vision). Starting these medicines
1477 may lessen how well LAMICTAL XR works.
 - 1478 • are pregnant or plan to become pregnant. It is not known if LAMICTAL XR will
1479 harm your unborn baby. If you become pregnant while taking LAMICTAL XR, talk
1480 to your healthcare provider about registering with the North American
1481 Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling
1482 1-888-233-2334. The purpose of this registry is to collect information about the
1483 safety of antiepileptic drugs during pregnancy.
 - 1484 • are breastfeeding. LAMICTAL XR passes into breast milk and may cause side
1485 effects in a breastfed baby. If you breastfeed while taking LAMICTAL XR, watch
1486 your baby closely for trouble breathing, episodes of temporarily stopping
1487 breathing, sleepiness, or poor sucking. Call your baby's healthcare provider right
1488 away if you see any of these problems. Talk to your healthcare provider about
1489 the best way to feed your baby if you take LAMICTAL XR.
- 1490 Tell your healthcare provider about all the medicines you take or if you are planning
1491 to take a new medicine, including prescription and non-prescription medicines,
1492 vitamins, and herbal supplements. If you use LAMICTAL XR with certain other
1493 medicines, they can affect each other, causing side effects.

1494
1495 **How should I take LAMICTAL XR?**

- 1496 • Take LAMICTAL XR exactly as prescribed.
- 1497 • Your healthcare provider may change your dose. Do not change your dose
1498 without talking to your healthcare provider.
- 1499 • Do not stop taking LAMICTAL XR without talking to your healthcare provider.
1500 Stopping LAMICTAL XR suddenly may cause serious problems. For example, if
1501 you have epilepsy and you stop taking LAMICTAL XR suddenly, you may have
1502 seizures that do not stop. Talk with your healthcare provider about how to stop
1503 LAMICTAL XR slowly.

- 1504 • If you miss a dose of LAMICTAL XR, take it as soon as you remember. If it is
1505 almost time for your next dose, just skip the missed dose. Take the next dose at
1506 your regular time. **Do not take 2 doses at the same time.**
- 1507 • If you take too much LAMICTAL XR, call your healthcare provider or your local
1508 Poison Control Center or go to the nearest hospital emergency room right away.
- 1509 • You may not feel the full effect of LAMICTAL XR for several weeks.
- 1510 • If you have epilepsy, tell your healthcare provider if your seizures get worse or if
1511 you have any new types of seizures.
- 1512 • LAMICTAL XR can be taken with or without food.
- 1513 • Do not chew, crush, or divide LAMICTAL XR.
- 1514 • Swallow LAMICTAL XR Tablets whole.
- 1515 • If you have trouble swallowing LAMICTAL XR Tablets, tell your healthcare
1516 provider because there may be another form of LAMICTAL you can take.
- 1517 • If you receive LAMICTAL XR in a blisterpack, examine the blisterpack before use.
1518 Do not use if blisters are torn, broken, or missing.

1519

1520 **What should I avoid while taking LAMICTAL XR?**

1521 Do not drive a car or operate complex, hazardous machinery until you know how
1522 LAMICTAL XR affects you.

1523

1524 **What are the possible side effects of LAMICTAL XR?**

1525 See "What is the most important information I should know about LAMICTAL XR?"

1526 Common side effects of LAMICTAL XR include:

- 1527 • dizziness
- 1528 • tremor
- 1529 • double vision
- 1530 • nausea
- 1531 • vomiting
- 1532 • trouble with balance and coordination
- 1533 • anxiety

1534 Other common side effects that have been reported with another form of LAMICTAL
1535 include headache, sleepiness, blurred vision, runny nose, and rash.

1536 Tell your healthcare provider about any side effect that bothers you or that does
1537 not go away.

1538 These are not all the possible side effects of LAMICTAL XR. For more information,
1539 ask your healthcare provider or pharmacist.

1540 Call your doctor for medical advice about side effects. You may report side effects
1541 to FDA at 1-800-FDA-1088.

1542

1543 **How should I store LAMICTAL XR?**

- 1544 • Store LAMICTAL XR at room temperature between 59°F and 86°F (15°C and
1545 30°C).
- 1546 • **Keep LAMICTAL XR and all medicines out of the reach of children.**

1547

1548 **General information about LAMICTAL XR**

1549 Medicines are sometimes prescribed for purposes other than those listed in a
1550 Medication Guide. Do not use LAMICTAL XR for a condition for which it was not
1551 prescribed. Do not give LAMICTAL XR to other people, even if they have the same
1552 symptoms you have. It may harm them.

1553 This Medication Guide summarizes the most important information about LAMICTAL
1554 XR. If you would like more information, talk with your healthcare provider. You can
1555 ask your healthcare provider or pharmacist for information about LAMICTAL XR that
1556 is written for healthcare professionals.

1557 For more information, go to www.lamictalxr.com or call 1-888-825-5249.

1558

1559 **What are the ingredients in LAMICTAL XR?**

1560 Active ingredient: lamotrigine.

1561 Inactive ingredients: glycerol monostearate, hypromellose, lactose monohydrate,
1562 magnesium stearate, methacrylic acid copolymer dispersion, polyethylene glycol
1563 400, polysorbate 80, silicon dioxide (25- and 50-mg tablets only), titanium dioxide,
1564 triethyl citrate, carmine (250-mg tablet only), iron oxide black (50-, 250-, and 300-
1565 mg tablets only), iron oxide yellow (25-, 50-, and 100-mg tablets only), iron oxide
1566 red (100-mg tablet only), FD&C Blue No. 2 Aluminum Lake (200- and 250-mg
1567 tablets only). Tablets are printed with edible black ink.

1568

1569 **This Medication Guide has been approved by the U.S. Food and Drug**
1570 **Administration.**

1571

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1573 listed are trademarks of their respective owners and are not trademarks of the GSK
1574 group of companies. The makers of these brands are not affiliated with and do not
1575 endorse the GSK group of companies or its products.

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Page 50



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