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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

LAMICTAL (lamotrigine) Tablets
LAMICTAL (lamotrigine) Chewable Dispersible Tablets
LAMICTAL ODT (lamotrigine) Orally Disintegrating Tablets
Initial U.S. Approval: 1994

WARNING: SERIOUS SKIN RASHES

See full prescribing information for complete boxed warning.

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

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

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

RECENT MAJOR CHANGES

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

INDICATIONS AND USAGE

LAMICTAL is an antiepileptic drug (AED) indicated for:

Epilepsy—adjunctive therapy in patients ≥ 2 years of age: (1.1)

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

Epilepsy—monotherapy in patients ≥ 16 years of age: conversion to monotherapy in patients with partial seizures who are receiving treatment with carbamazepine, phenobarbital, phenytoin, primidone, or valproate as the single AED. (1.1)

Bipolar Disorder in patients ≥ 18 years of age: maintenance treatment of Bipolar I Disorder to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy. (1.2)

DOSAGE AND ADMINISTRATION

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

Epilepsy

- Adjunctive therapy—See Table 1 for patients >12 years of age and Tables 2 and 3 for patients 2 to 12 years. (2.2)
- Conversion to monotherapy—See Table 4. (2.3)

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

DOSAGE FORMS AND STRENGTHS

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

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised:

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

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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 (2 to 16 years
6 of age) receiving LAMICTAL as adjunctive therapy for epilepsy and 0.3% (3 per 1,000) in
7 adults on adjunctive therapy for epilepsy. In clinical trials of bipolar and other mood
8 disorders, the rate of serious rash was 0.08% (0.8 per 1,000) in adult patients receiving
9 LAMICTAL as initial monotherapy and 0.13% (1.3 per 1,000) in adult patients receiving
10 LAMICTAL as adjunctive therapy. In a prospectively followed cohort of 1,983 pediatric
11 patients (2 to 16 years of age) with epilepsy taking adjunctive LAMICTAL, there was 1
12 rash-related death. In worldwide postmarketing experience, rare cases of toxic epidermal
13 necrolysis and/or rash-related death have been reported in adult and pediatric patients, but
14 their numbers are too few to permit a precise estimate of the rate.

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

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

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

30 1 INDICATIONS AND USAGE

31 1.1 Epilepsy

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

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

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

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

44 **1.2 Bipolar Disorder**

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

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

54 **2 DOSAGE AND ADMINISTRATION**

55 **2.1 General Dosing Considerations**

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

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

65 LAMICTAL Starter Kits and LAMICTAL[®] 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 (> 12 years of age) and
68 Bipolar I Disorder (≥ 18 years of age) and are intended to help reduce the potential for rash. The
69 use of LAMICTAL Starter Kits and LAMICTAL ODT Patient Titration Kits is recommended
70 for appropriate patients who are starting or restarting LAMICTAL [*see How Supplied/Storage*
71 *and Handling (16)*].

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

175 **2.2 Epilepsy – Adjunctive Therapy**

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

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

184

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

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

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

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

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

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

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

210

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

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

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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

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

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

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

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

226

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

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

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

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

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

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

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

251

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

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

254

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

260 **2.4 Bipolar Disorder**

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

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

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

282 To avoid an increased risk of rash, the recommended initial dose and subsequent dose
283 escalations of LAMICTAL should not be exceeded [*see Boxed Warning*].
284

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

	For Patients TAKING Valproate ^a	For Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone, ^b or Valproate ^a	For Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone ^b and NOT TAKING Valproate ^a
Weeks 1 and 2	25 mg every <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

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

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

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

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

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

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

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

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

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

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

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

325 **3 DOSAGE FORMS AND STRENGTHS**

326 **3.1 Tablets**

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

331 **3.2 Chewable Dispersible Tablets**

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

335 **3.3 Orally Disintegrating Tablets**

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

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

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

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

344 **3.4 Potential Medication Errors**

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

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349 **4 CONTRAINDICATIONS**

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

352 **5 WARNINGS AND PRECAUTIONS**

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

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

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

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

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

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

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

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

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

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

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

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

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

409 **5.3 Blood Dyscrasias**

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

414 **5.4 Suicidal Behavior and Ideation**

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

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

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

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

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

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

438

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

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

440

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

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

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

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

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

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

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

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

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

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

479 **5.6 Aseptic Meningitis**

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

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

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

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

501 **5.7 Potential Medication Errors**

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

513 **5.8 Concomitant Use With Oral Contraceptives**

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

521 **5.9 Withdrawal Seizures**

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

529 **5.10 Status Epilepticus**

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

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

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

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

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

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

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

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

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

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

567 **5.14 Laboratory Tests**

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

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

574 **6 ADVERSE REACTIONS**

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

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

585 **6.1 Clinical Trials**

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

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

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

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

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

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

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

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

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

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

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

644

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

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

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

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

653

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

657

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

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

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

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

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662

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

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

678

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

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

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Nervous		
Coordination abnormality	7	0
Dizziness	7	0
Anxiety	5	0
Insomnia	5	2
Respiratory		
Rhinitis	7	2
Urogenital (female patients only)	(n = 21)	(n = 28)
Dysmenorrhea	5	0

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

686 ^b Up to 500 mg/day.

687 ^c 1,000 mg/day.

688

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

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

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

693 *Metabolic and Nutritional:* Peripheral edema.

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

696 *Respiratory:* Epistaxis, bronchitis, dyspnea.

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

698 *Special Senses:* Vision abnormality.

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

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

704

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

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

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Nervous system		
Somnolence	17	15
Dizziness	14	4
Ataxia	11	3
Tremor	10	1
Emotional lability	4	2
Gait abnormality	4	2
Thinking abnormality	3	2
Convulsions	2	1
Nervousness	2	1
Vertigo	2	1
Respiratory		
Pharyngitis	14	11
Bronchitis	7	5
Increased cough	7	6
Sinusitis	2	1
Bronchospasm	2	1
Skin		
Rash	14	12
Eczema	2	1
Pruritus	2	1
Special senses		
Diplopia	5	1
Blurred vision	4	1
Visual abnormality	2	0
Urogenital		
Male and female patients		
Urinary tract infection	3	0

709

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

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

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

730

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

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

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

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

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

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

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

749 *General:* Fever, neck pain.

750 *Cardiovascular:* Migraine.

751 *Digestive:* Flatulence.

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

753 *Musculoskeletal:* Arthralgia, myalgia.

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

756 *Respiratory:* Sinusitis.

757 *Urogenital:* Urinary frequency.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

827 **6.3 Postmarketing Experience**

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

832 Blood and Lymphatic: Agranulocytosis, hemolytic anemia.

833 Gastrointestinal: Esophagitis.

834 Hepatobiliary Tract and Pancreas: Pancreatitis.

835 Immunologic: Lupus-like reaction, vasculitis.

836 Lower Respiratory: Apnea.

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

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

841 Non-site Specific: Progressive immunosuppression.

842 **7 DRUG INTERACTIONS**

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

846

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

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

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

848 ↓ = Decreased (induces lamotrigine glucuronidation).

849 ↑ = Increased (inhibits lamotrigine glucuronidation).

850 ? = Conflicting data.

851 **8 USE IN SPECIFIC POPULATIONS**

852 **8.1 Pregnancy**

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

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

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865 rearing. In a swimming maze test performed on days 39 to 44 postpartum, time to completion
866 was increased in offspring of dams receiving 25 mg/kg/day. These doses represent 0.1 and 0.5
867 times the clinical dose on a mg/m² basis, respectively.

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

871 When pregnant rats were orally dosed at 0.1, 0.14, or 0.3 times the highest human
872 maintenance dose (on a mg/m² basis) during the latter part of gestation (days 15 to 20), maternal
873 toxicity and fetal death were seen. In dams, food consumption and weight gain were reduced,
874 and the gestation period was slightly prolonged (22.6 vs. 22.0 days in the control group).
875 Stillborn pups were found in all 3 drug-treated groups with the highest number in the high-dose
876 group. Postnatal death was also seen, but only in the 2 highest doses, and occurred between days
877 1 and 20. Some of these deaths appear to be drug-related and not secondary to the maternal
878 toxicity. A no-observed-effect level (NOEL) could not be determined for this study.

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

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

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

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

900 **8.2 Labor and Delivery**

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

902 **8.3 Nursing Mothers**

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

916 **8.4 Pediatric Use**

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

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

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

930 **8.5 Geriatric Use**

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

937 **8.6 Patients With Hepatic Impairment**

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

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

946 **8.7 Patients With Renal Impairment**

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

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

957 **10 OVERDOSAGE**

958 **10.1 Human Overdose Experience**

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

962 **10.2 Management of Overdose**

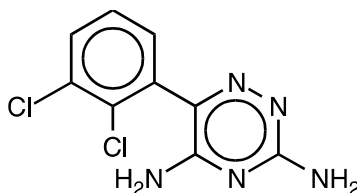
963 There are no specific antidotes for lamotrigine. Following a suspected overdose,
964 hospitalization of the patient is advised. General supportive care is indicated, including frequent
965 monitoring of vital signs and close observation of the patient. If indicated, emesis should be
966 induced;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

972 **11 DESCRIPTION**

973 LAMICTAL (lamotrigine), an AED of the phenyltriazine class, is chemically unrelated to
974 existing AEDs. Its chemical name is 3,5-diamino-6-(2,3-dichlorophenyl)-*as*-triazine, its
975 molecular formula is C₉H₇N₅Cl₂, and its molecular weight is 256.09. Lamotrigine is a white to
976 pale cream-colored powder and has a pK_a of 5.7. Lamotrigine is very slightly soluble in water
977 (0.17 mg/mL at 25°C) and slightly soluble in 0.1 M HCl (4.1 mg/mL at 25°C). The structural
978 formula is:

979

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980
981

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

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

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

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

1001 **12 CLINICAL PHARMACOLOGY**

1002 **12.1 Mechanism of Action**

1003 The precise mechanism(s) by which lamotrigine exerts its anticonvulsant action are
1004 unknown. In animal models designed to detect anticonvulsant activity, lamotrigine was effective
1005 in preventing seizure spread in the maximum electroshock (MES) and pentylenetetrazol (scMet)
1006 tests, and prevented seizures in the visually and electrically evoked after-discharge (EEAD) tests
1007 for antiepileptic activity. Lamotrigine also displayed inhibitory properties in the kindling model
1008 in rats both during kindling development and in the fully kindled state. The relevance of these
1009 models to human epilepsy, however, is not known.

1010 One proposed mechanism of action of lamotrigine, the relevance of which remains to be
1011 established in humans, involves an effect on sodium channels. In vitro pharmacological studies
1012 suggest that lamotrigine inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal
1013 membranes and consequently modulating presynaptic transmitter release of excitatory amino
1014 acids (e.g., glutamate and aspartate).

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1015 Although the relevance for human use is unknown, the following data characterize the
1016 performance of lamotrigine in receptor binding assays. Lamotrigine had a weak inhibitory effect
1017 on the serotonin 5-HT₃ receptor (IC₅₀ = 18 μM). It does not exhibit high affinity binding
1018 (IC₅₀>100 μM) to the following neurotransmitter receptors: adenosine A₁ and A₂; adrenergic α₁,
1019 α₂, and β; dopamine D₁ and D₂; γ-aminobutyric acid (GABA) A and B; histamine H₁; kappa
1020 opioid; muscarinic acetylcholine; and serotonin 5-HT₂. Studies have failed to detect an effect of
1021 lamotrigine on dihydropyridine-sensitive calcium channels. It had weak effects at sigma opioid
1022 receptors (IC₅₀ = 145 μM). Lamotrigine did not inhibit the uptake of norepinephrine, dopamine,
1023 or serotonin (IC₅₀>200 μM) when tested in rat synaptosomes and/or human platelets in vitro.

1024 Effect of Lamotrigine on N-Methyl d-Aspartate-Receptor Mediated Activity:
1025 Lamotrigine did not inhibit N-methyl d-aspartate (NMDA)-induced depolarizations in rat cortical
1026 slices or NMDA-induced cyclic GMP formation in immature rat cerebellum, nor did lamotrigine
1027 displace compounds that are either competitive or noncompetitive ligands at this glutamate
1028 receptor complex (CNQX, CGS, TCHP). The IC₅₀ for lamotrigine effects on NMDA-induced
1029 currents (in the presence of 3 μM of glycine) in cultured hippocampal neurons exceeded 100
1030 μM.

1031 The mechanisms by which lamotrigine exerts its therapeutic action in Bipolar Disorder
1032 have not been established.

1033 **12.2 Pharmacodynamics**

1034 Folate Metabolism: In vitro, lamotrigine inhibited dihydrofolate reductase, the enzyme
1035 that catalyzes the reduction of dihydrofolate to tetrahydrofolate. Inhibition of this enzyme may
1036 interfere with the biosynthesis of nucleic acids and proteins. When oral daily doses of
1037 lamotrigine were given to pregnant rats during organogenesis, fetal, placental, and maternal
1038 folate concentrations were reduced. Significantly reduced concentrations of folate are associated
1039 with teratogenesis [see *Use in Specific Populations (8.1)*]. Folate concentrations were also
1040 reduced in male rats given repeated oral doses of lamotrigine. Reduced concentrations were
1041 partially returned to normal when supplemented with folic acid.

1042 Accumulation in Kidneys: Lamotrigine accumulated in the kidney of the male rat,
1043 causing chronic progressive nephrosis, necrosis, and mineralization. These findings are attributed
1044 to α-2 microglobulin, a species- and sex-specific protein that has not been detected in humans or
1045 other animal species.

1046 Melanin Binding: Lamotrigine binds to melanin-containing tissues, e.g., in the eye and
1047 pigmented skin. It has been found in the uveal tract up to 52 weeks after a single dose in rodents.

1048 Cardiovascular: In dogs, lamotrigine is extensively metabolized to a 2-N-methyl
1049 metabolite. This metabolite causes dose-dependent prolongations of the PR interval, widening of
1050 the QRS complex, and, at higher doses, complete AV conduction block. Similar cardiovascular
1051 effects are not anticipated in humans because only trace amounts of the 2-N-methyl metabolite
1052 (<0.6% of lamotrigine dose) have been found in human urine [see *Clinical Pharmacology*
1053 (12.3)]. However, it is conceivable that plasma concentrations of this metabolite could be

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1054 increased in patients with a reduced capacity to glucuronidate lamotrigine (e.g., in patients with
1055 liver disease).

1056 **12.3 Pharmacokinetics**

1057 The pharmacokinetics of lamotrigine have been studied in patients with epilepsy, healthy
1058 young and elderly volunteers, and volunteers with chronic renal failure. Lamotrigine
1059 pharmacokinetic parameters for adult and pediatric patients and healthy normal volunteers are
1060 summarized in Tables 14 and 16.

1061

1062 **Table 14. Mean^a Pharmacokinetic Parameters in Healthy Volunteers and Adult Patients**
1063 **With Epilepsy**

Adult Study Population	Number of Subjects	T _{max} : Time of Maximum Plasma Concentration (hr)	t _{1/2} : Elimination Half-life (hr)	Cl/F: Apparent Plasma Clearance (mL/min/kg)
Healthy volunteers taking no other medications:				
Single-dose LAMICTAL	179	2.2 (0.25-12.0)	32.8 (14.0-103.0)	0.44 (0.12-1.10)
Multiple-dose LAMICTAL	36	1.7 (0.5-4.0)	25.4 (11.6-61.6)	0.58 (0.24-1.15)
Healthy volunteers taking valproate:				
Single-dose LAMICTAL	6	1.8 (1.0-4.0)	48.3 (31.5-88.6)	0.30 (0.14-0.42)
Multiple-dose LAMICTAL	18	1.9 (0.5-3.5)	70.3 (41.9-113.5)	0.18 (0.12-0.33)
Patients with epilepsy taking valproate only:				
Single-dose LAMICTAL	4	4.8 (1.8-8.4)	58.8 (30.5-88.8)	0.28 (0.16-0.40)
Patients with epilepsy taking carbamazepine, phenytoin, phenobarbital, or primidone^b plus valproate:				
Single-dose LAMICTAL	25	3.8 (1.0-10.0)	27.2 (11.2-51.6)	0.53 (0.27-1.04)

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Patients with epilepsy taking carbamazepine, phenytoin, phenobarbital, or primidone:^b				
Single-dose LAMICTAL	24	2.3 (0.5-5.0)	14.4 (6.4-30.4)	1.10 (0.51-2.22)
Multiple-dose LAMICTAL	17	2.0 (0.75-5.93)	12.6 (7.5-23.1)	1.21 (0.66-1.82)

1064 ^a The majority of parameter means determined in each study had coefficients of variation
1065 between 20% and 40% for half-life and C₁/F and between 30% and 70% for T_{max}. The overall
1066 mean values were calculated from individual study means that were weighted based on the
1067 number of volunteers/patients in each study. The numbers in parentheses below each
1068 parameter mean represent the range of individual volunteer/patient values across studies.

1069 ^b Carbamazepine, phenobarbital, phenytoin, and primidone have been shown to increase the
1070 apparent clearance of lamotrigine. Estrogen-containing oral contraceptives and other drugs
1071 such as rifampin that induce lamotrigine glucuronidation have also been shown to increase the
1072 apparent clearance of lamotrigine [see *Drug Interactions (7)*].
1073

1074 **Absorption:** Lamotrigine is rapidly and completely absorbed after oral administration
1075 with negligible first-pass metabolism (absolute bioavailability is 98%). The bioavailability is not
1076 affected by food. Peak plasma concentrations occur anywhere from 1.4 to 4.8 hours following
1077 drug administration. The lamotrigine chewable/dispersible tablets were found to be equivalent,
1078 whether they were administered as dispersed in water, chewed and swallowed, or swallowed as
1079 whole, to the lamotrigine compressed tablets in terms of rate and extent of absorption. In terms
1080 of rate and extent of absorption, lamotrigine orally disintegrating tablets whether disintegrated in
1081 the mouth or swallowed whole with water were equivalent to the lamotrigine compressed tablets
1082 swallowed with water.

1083 **Dose Proportionality:** In healthy volunteers not receiving any other medications and
1084 given single doses, the plasma concentrations of lamotrigine increased in direct proportion to the
1085 dose administered over the range of 50 to 400 mg. In 2 small studies (n = 7 and 8) of patients
1086 with epilepsy who were maintained on other AEDs, there also was a linear relationship between
1087 dose and lamotrigine plasma concentrations at steady state following doses of 50 to 350 mg
1088 twice daily.

1089 **Distribution:** Estimates of the mean apparent volume of distribution (V_d/F) of
1090 lamotrigine following oral administration ranged from 0.9 to 1.3 L/kg. V_d/F is independent of
1091 dose and is similar following single and multiple doses in both patients with epilepsy and in
1092 healthy volunteers.

1093 **Protein Binding:** Data from in vitro studies indicate that lamotrigine is approximately
1094 55% bound to human plasma proteins at plasma lamotrigine concentrations from 1 to 10 mcg/mL
1095 (10 mcg/mL is 4 to 6 times the trough plasma concentration observed in the controlled efficacy

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1096 trials). Because lamotrigine is not highly bound to plasma proteins, clinically significant
1097 interactions with other drugs through competition for protein binding sites are unlikely. The
1098 binding of lamotrigine to plasma proteins did not change in the presence of therapeutic
1099 concentrations of phenytoin, phenobarbital, or valproate. Lamotrigine did not displace other
1100 AEDs (carbamazepine, phenytoin, phenobarbital) from protein-binding sites.

1101 **Metabolism:** Lamotrigine is metabolized predominantly by glucuronic acid conjugation;
1102 the major metabolite is an inactive 2-N-glucuronide conjugate. After oral administration of 240
1103 mg of ¹⁴C-lamotrigine (15 μCi) to 6 healthy volunteers, 94% was recovered in the urine and 2%
1104 was recovered in the feces. The radioactivity in the urine consisted of unchanged lamotrigine
1105 (10%), the 2-N-glucuronide (76%), a 5-N-glucuronide (10%), a 2-N-methyl metabolite (0.14%),
1106 and other unidentified minor metabolites (4%).

1107 **Enzyme Induction:** The effects of lamotrigine on the induction of specific families of
1108 mixed-function oxidase isozymes have not been systematically evaluated.

1109 Following multiple administrations (150 mg twice daily) to normal volunteers taking no
1110 other medications, lamotrigine induced its own metabolism, resulting in a 25% decrease in t_{1/2} and
1111 a 37% increase in Cl/F at steady state compared with values obtained in the same volunteers
1112 following a single dose. Evidence gathered from other sources suggests that self-induction by
1113 lamotrigine may not occur when lamotrigine is given as adjunctive therapy in patients receiving
1114 enzyme-inducing drugs such as carbamazepine, phenytoin, phenobarbital, primidone, or drugs
1115 such as rifampin that induce lamotrigine glucuronidation [*see Drug Interactions (7)*].

1116 **Elimination:** The elimination half-life and apparent clearance of lamotrigine following
1117 administration of LAMICTAL to adult patients with epilepsy and healthy volunteers is
1118 summarized in Table 14. Half-life and apparent oral clearance vary depending on concomitant
1119 AEDs.

1120 **Drug Interactions:** The apparent clearance of lamotrigine is affected by the
1121 coadministration of certain medications [*see Warnings and Precautions (5.8, 5.12), Drug*
1122 *Interactions (7)*].

1123 The net effects of drug interactions with LAMICTAL are summarized in Tables 13 and
1124 15, followed by details of the drug interaction studies below.

1125

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1126 **Table 15. Summary of Drug Interactions With LAMICTAL**

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

1127 ^a From adjunctive clinical trials and volunteer studies.

1128 ^b Net effects were estimated by comparing the mean clearance values obtained in adjunctive
1129 clinical trials and volunteer studies.

1130 ^c The effect of other hormonal contraceptive preparations or hormone replacement therapy on
1131 the pharmacokinetics of lamotrigine has not been systematically evaluated in clinical trials,
1132 although the effect may be similar to that seen with the ethinylestradiol/levonorgestrel
1133 combinations.

1134 ^d Modest decrease in levonorgestrel.

1135 ^e Not administered, but an active metabolite of carbamazepine.

1136 ^f Slight decrease, not expected to be clinically relevant.

1137 ^g Not administered, but an active metabolite of oxcarbazepine.

1138 ^h Slight increase, not expected to be clinically relevant.

1139 ↔ = No significant effect.

1140 ? = Conflicting data.

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1141

1142 **Estrogen-Containing Oral Contraceptives:** In 16 female volunteers, an oral
1143 contraceptive preparation containing 30 mcg ethinylestradiol and 150 mcg levonorgestrel
1144 increased the apparent clearance of lamotrigine (300 mg/day) by approximately 2-fold with mean
1145 decreases in AUC of 52% and in C_{max} of 39%. In this study, trough serum lamotrigine
1146 concentrations gradually increased and were approximately 2-fold higher on average at the end
1147 of the week of the inactive hormone preparation compared with trough lamotrigine
1148 concentrations at the end of the active hormone cycle.

1149 Gradual transient increases in lamotrigine plasma levels (approximate 2-fold increase)
1150 occurred during the week of inactive hormone preparation (“pill-free” week) for women not also
1151 taking a drug that increased the clearance of lamotrigine (carbamazepine, phenytoin,
1152 phenobarbital, primidone, or other drugs such as rifampin that induce lamotrigine
1153 glucuronidation [*see Drug Interactions (7)*]). The increase in lamotrigine plasma levels will be
1154 greater if the dose of LAMICTAL is increased in the few days before or during the “pill-free”
1155 week. Increases in lamotrigine plasma levels could result in dose-dependent adverse reactions.

1156 In the same study, coadministration of LAMICTAL (300 mg/day) in 16 female
1157 volunteers did not affect the pharmacokinetics of the ethinylestradiol component of the oral
1158 contraceptive preparation. There were mean decreases in the AUC and C_{max} of the levonorgestrel
1159 component of 19% and 12%, respectively. Measurement of serum progesterone indicated that
1160 there was no hormonal evidence of ovulation in any of the 16 volunteers, although measurement
1161 of serum FSH, LH, and estradiol indicated that there was some loss of suppression of the
1162 hypothalamic-pituitary-ovarian axis.

1163 The effects of doses of LAMICTAL other than 300 mg/day have not been systematically
1164 evaluated in controlled clinical trials.

1165 The clinical significance of the observed hormonal changes on ovulatory activity is
1166 unknown. However, the possibility of decreased contraceptive efficacy in some patients cannot
1167 be excluded. Therefore, patients should be instructed to promptly report changes in their
1168 menstrual pattern (e.g., break-through bleeding).

1169 Dosage adjustments may be necessary for women receiving estrogen-containing oral
1170 contraceptive preparations [*see Dosage and Administration (2.1)*].

1171 **Other Hormonal Contraceptives or Hormone Replacement Therapy:** The effect of
1172 other hormonal contraceptive preparations or hormone replacement therapy on the
1173 pharmacokinetics of lamotrigine has not been systematically evaluated. It has been reported that
1174 ethinylestradiol, not progestogens, increased the clearance of lamotrigine up to 2-fold, and the
1175 progestin-only pills had no effect on lamotrigine plasma levels. Therefore, adjustments to the
1176 dosage of LAMICTAL in the presence of progestogens alone will likely not be needed.

1177 **Bupropion:** The pharmacokinetics of a 100-mg single dose of LAMICTAL in healthy
1178 volunteers (n = 12) were not changed by coadministration of bupropion sustained-release
1179 formulation (150 mg twice daily) starting 11 days before LAMICTAL.

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1180 **Carbamazepine:** LAMICTAL has no appreciable effect on steady-state carbamazepine
1181 plasma concentration. Limited clinical data suggest there is a higher incidence of dizziness,
1182 diplopia, ataxia, and blurred vision in patients receiving carbamazepine with lamotrigine than in
1183 patients receiving other AEDs with lamotrigine [see *Adverse Reactions (6.1)*]. The mechanism
1184 of this interaction is unclear. The effect of lamotrigine on plasma concentrations of
1185 carbamazepine-epoxide is unclear. In a small subset of patients (n = 7) studied in a placebo-
1186 controlled trial, lamotrigine had no effect on carbamazepine-epoxide plasma concentrations, but
1187 in a small, uncontrolled study (n = 9), carbamazepine-epoxide levels increased.

1188 The addition of carbamazepine decreases lamotrigine steady-state concentrations by
1189 approximately 40%.

1190 **Felbamate:** In a study of 21 healthy volunteers, coadministration of felbamate (1,200 mg
1191 twice daily) with lamotrigine (100 mg twice daily for 10 days) appeared to have no clinically
1192 relevant effects on the pharmacokinetics of lamotrigine.

1193 **Folate Inhibitors:** Lamotrigine is a weak inhibitor of dihydrofolate reductase. Prescribers
1194 should be aware of this action when prescribing other medications that inhibit folate metabolism.

1195 **Gabapentin:** Based on a retrospective analysis of plasma levels in 34 patients who
1196 received lamotrigine both with and without gabapentin, gabapentin does not appear to change the
1197 apparent clearance of lamotrigine.

1198 **Levetiracetam:** Potential drug interactions between levetiracetam and lamotrigine were
1199 assessed by evaluating serum concentrations of both agents during placebo-controlled clinical
1200 trials. These data indicate that lamotrigine does not influence the pharmacokinetics of
1201 levetiracetam and that levetiracetam does not influence the pharmacokinetics of lamotrigine.

1202 **Lithium:** The pharmacokinetics of lithium were not altered in healthy subjects (n = 20) by
1203 coadministration of lamotrigine (100 mg/day) for 6 days.

1204 **Olanzapine:** The AUC and C_{max} of olanzapine were similar following the addition of
1205 olanzapine (15 mg once daily) to lamotrigine (200 mg once daily) in healthy male volunteers (n
1206 = 16) compared with the AUC and C_{max} in healthy male volunteers receiving olanzapine alone (n
1207 = 16).

1208 In the same study, the AUC and C_{max} of lamotrigine were reduced on average by 24%
1209 and 20%, respectively, following the addition of olanzapine to lamotrigine in healthy male
1210 volunteers compared with those receiving lamotrigine alone. This reduction in lamotrigine
1211 plasma concentrations is not expected to be clinically relevant.

1212 **Oxcarbazepine:** The AUC and C_{max} of oxcarbazepine and its active 10-monohydroxy
1213 oxcarbazepine metabolite were not significantly different following the addition of
1214 oxcarbazepine (600 mg twice daily) to lamotrigine (200 mg once daily) in healthy male
1215 volunteers (n = 13) compared with healthy male volunteers receiving oxcarbazepine alone (n =
1216 13).

1217 In the same study, the AUC and C_{max} of lamotrigine were similar following the addition
1218 of oxcarbazepine (600 mg twice daily) to LAMICTAL in healthy male volunteers compared with

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1219 those receiving LAMICTAL alone. Limited clinical data suggest a higher incidence of headache,
1220 dizziness, nausea, and somnolence with coadministration of lamotrigine and oxcarbazepine
1221 compared with lamotrigine alone or oxcarbazepine alone.

1222 Phenobarbital, Primidone: The addition of phenobarbital or primidone decreases
1223 lamotrigine steady-state concentrations by approximately 40%.

1224 Phenytoin: Lamotrigine has no appreciable effect on steady-state phenytoin plasma
1225 concentrations in patients with epilepsy. The addition of phenytoin decreases lamotrigine steady-
1226 state concentrations by approximately 40%.

1227 Pregabalin: Steady-state trough plasma concentrations of lamotrigine were not affected
1228 by concomitant pregabalin (200 mg 3 times daily) administration. There are no pharmacokinetic
1229 interactions between lamotrigine and pregabalin.

1230 Rifampin: In 10 male volunteers, rifampin (600 mg/day for 5 days) significantly
1231 increased the apparent clearance of a single 25-mg dose of lamotrigine by approximately 2-fold
1232 (AUC decreased by approximately 40%).

1233 Topiramate: Topiramate resulted in no change in plasma concentrations of lamotrigine.
1234 Administration of lamotrigine resulted in a 15% increase in topiramate concentrations.

1235 Valproate: When lamotrigine was administered to healthy volunteers (n = 18) receiving
1236 valproate, the trough steady-state valproate plasma concentrations decreased by an average of
1237 25% over a 3-week period, and then stabilized. However, adding lamotrigine to the existing
1238 therapy did not cause a change in valproate plasma concentrations in either adult or pediatric
1239 patients in controlled clinical trials.

1240 The addition of valproate increased lamotrigine steady-state concentrations in normal
1241 volunteers by slightly more than 2-fold. In one study, maximal inhibition of lamotrigine
1242 clearance was reached at valproate doses between 250 and 500 mg/day and did not increase as
1243 the valproate dose was further increased.

1244 Zonisamide: In a study of 18 patients with epilepsy, coadministration of zonisamide
1245 (200 to 400 mg/day) with lamotrigine (150 to 500 mg/day for 35 days) had no significant effect
1246 on the pharmacokinetics of lamotrigine.

1247 Known Inducers or Inhibitors of Glucuronidation: Drugs other than those listed above
1248 have not been systematically evaluated in combination with lamotrigine. Since lamotrigine is
1249 metabolized predominately by glucuronic acid conjugation, drugs that are known to induce or
1250 inhibit glucuronidation may affect the apparent clearance of lamotrigine and doses of lamotrigine
1251 may require adjustment based on clinical response.

1252 Other: Results of in vitro experiments suggest that clearance of lamotrigine is unlikely to
1253 be reduced by concomitant administration of amitriptyline, clonazepam, clozapine, fluoxetine,
1254 haloperidol, lorazepam, phenelzine, risperidone, sertraline, or trazodone.

1255 Results of in vitro experiments suggest that lamotrigine does not reduce the clearance of
1256 drugs eliminated predominantly by CYP2D6.

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1257 **Special Populations: Patients With Renal Impairment:** Twelve volunteers with
1258 chronic renal failure (mean creatinine clearance: 13 mL/min, range: 6 to 23) and another 6
1259 individuals undergoing hemodialysis were each given a single 100-mg dose of lamotrigine. The
1260 mean plasma half-lives determined in the study were 42.9 hours (chronic renal failure), 13.0
1261 hours (during hemodialysis), and 57.4 hours (between hemodialysis) compared with 26.2 hours
1262 in healthy volunteers. On average, approximately 20% (range: 5.6 to 35.1) of the amount of
1263 lamotrigine present in the body was eliminated by hemodialysis during a 4-hour session [*see*
1264 *Dosage and Administration (2.1)*].

1265 **Hepatic Disease:** The pharmacokinetics of lamotrigine following a single 100-mg
1266 dose of lamotrigine were evaluated in 24 subjects with mild, moderate, and severe hepatic
1267 impairment (Child-Pugh Classification system) and compared with 12 subjects without hepatic
1268 impairment. The patients with severe hepatic impairment were without ascites (n = 2) or with
1269 ascites (n = 5). The mean apparent clearances of lamotrigine in patients with mild (n = 12),
1270 moderate (n = 5), severe without ascites (n = 2), and severe with ascites (n = 5) liver impairment
1271 were 0.30 ± 0.09 , 0.24 ± 0.1 , 0.21 ± 0.04 , and 0.15 ± 0.09 mL/min/kg, respectively, as compared
1272 with 0.37 ± 0.1 mL/min/kg in the healthy controls. Mean half-lives of lamotrigine in patients
1273 with mild, moderate, severe without ascites, and severe with ascites hepatic impairment were 46
1274 ± 20 , 72 ± 44 , 67 ± 11 , and 100 ± 48 hours, respectively, as compared with 33 ± 7 hours in
1275 healthy controls [*see Dosage and Administration (2.1)*].

1276 **Age: Pediatric Patients:** The pharmacokinetics of lamotrigine following a single 2-
1277 mg/kg dose were evaluated in 2 studies of pediatric patients (n = 29 for patients 10 months to 5.9
1278 years of age and n = 26 for patients 5 to 11 years of age). Forty-three patients received
1279 concomitant therapy with other AEDs and 12 patients received lamotrigine as monotherapy.
1280 Lamotrigine pharmacokinetic parameters for pediatric patients are summarized in Table 16.

1281 Population pharmacokinetic analyses involving patients 2 to 18 years of age
1282 demonstrated that lamotrigine clearance was influenced predominantly by total body weight and
1283 concurrent AED therapy. The oral clearance of lamotrigine was higher, on a body weight basis,
1284 in pediatric patients than in adults. Weight-normalized lamotrigine clearance was higher in those
1285 subjects weighing less than 30 kg, compared with those weighing greater than 30 kg.
1286 Accordingly, patients weighing less than 30 kg may need an increase of as much as 50% in
1287 maintenance doses, based on clinical response, as compared with subjects weighing more than
1288 30 kg being administered the same AEDs [*see Dosage and Administration (2.2)*]. These analyses
1289 also revealed that, after accounting for body weight, lamotrigine clearance was not significantly
1290 influenced by age. Thus, the same weight-adjusted doses should be administered to children
1291 irrespective of differences in age. Concomitant AEDs which influence lamotrigine clearance in
1292 adults were found to have similar effects in children.
1293

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Table 16. Mean Pharmacokinetic Parameters in Pediatric Patients With Epilepsy

Pediatric Study Population	Number of Subjects	T _{max} (hr)	t _{1/2} (hr)	Cl/F (mL/min/kg)
Ages 10 months-5.3 years				
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone ^a	10	3.0 (1.0-5.9)	7.7 (5.7-11.4)	3.62 (2.44-5.28)
Patients taking AEDs with no known effect on the apparent clearance of lamotrigine	7	5.2 (2.9-6.1)	19.0 (12.9-27.1)	1.2 (0.75-2.42)
Patients taking valproate only	8	2.9 (1.0-6.0)	44.9 (29.5-52.5)	0.47 (0.23-0.77)
Ages 5-11 years				
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone ^a	7	1.6 (1.0-3.0)	7.0 (3.8-9.8)	2.54 (1.35-5.58)
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone ^a plus valproate	8	3.3 (1.0-6.4)	19.1 (7.0-31.2)	0.89 (0.39-1.93)
Patients taking valproate only ^b	3	4.5 (3.0-6.0)	65.8 (50.7-73.7)	0.24 (0.21-0.26)
Ages 13-18 years				
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone ^a	11	c	c	1.3
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone ^a plus valproate	8	c	c	0.5
Patients taking valproate only	4	c	c	0.3

1295 ^a Carbamazepine, phenobarbital, phenytoin, and primidone have been shown to increase the
1296 apparent clearance of lamotrigine. Estrogen-containing oral contraceptives and rifampin have
1297 also been shown to increase the apparent clearance of lamotrigine [see *Drug Interactions (7)*].

1298 ^b Two subjects were included in the calculation for mean T_{max}.

1299 ^c Parameter not estimated.

1300

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

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1304 in these subjects was 31.2 hours (range: 24.5 to 43.4 hours), and the mean clearance was 0.40
1305 mL/min/kg (range: 0.26 to 0.48 mL/min/kg).

1306 *Gender:* The clearance of lamotrigine is not affected by gender. However, during
1307 dose escalation of LAMICTAL in one clinical trial in patients with epilepsy on a stable dose of
1308 valproate (n = 77), mean trough lamotrigine concentrations, unadjusted for weight, were 24% to
1309 45% higher (0.3 to 1.7 mcg/mL) in females than in males.

1310 *Race:* The apparent oral clearance of lamotrigine was 25% lower in non-Caucasians
1311 than Caucasians.

1312 **13 NONCLINICAL TOXICOLOGY**

1313 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

1314 No evidence of carcinogenicity was seen in 1 mouse study or 2 rat studies following oral
1315 administration of lamotrigine for up to 2 years at maximum tolerated doses (30 mg/kg/day for
1316 mice and 10 to 15 mg/kg/day for rats, doses that are equivalent to 90 mg/m² and 60 to 90 mg/m²,
1317 respectively). Steady-state plasma concentrations ranged from 1 to 4 mcg/mL in the mouse study
1318 and 1 to 10 mcg/mL in the rat study. Plasma concentrations associated with the recommended
1319 human doses of 300 to 500 mg/day are generally in the range of 2 to 5 mcg/mL, but
1320 concentrations as high as 19 mcg/mL have been recorded.

1321 Lamotrigine was not mutagenic in the presence or absence of metabolic activation when
1322 tested in 2 gene mutation assays (the Ames test and the in vitro mammalian mouse lymphoma
1323 assay). In 2 cytogenetic assays (the in vitro human lymphocyte assay and the in vivo rat bone
1324 marrow assay), lamotrigine did not increase the incidence of structural or numerical
1325 chromosomal abnormalities.

1326 No evidence of impairment of fertility was detected in rats given oral doses of
1327 lamotrigine up to 2.4 times the highest usual human maintenance dose of 8.33 mg/kg/day or 0.4
1328 times the human dose on a mg/m² basis. The effect of lamotrigine on human fertility is unknown.

1329 **14 CLINICAL STUDIES**

1330 **14.1 Epilepsy**

1331 Monotherapy With LAMICTAL in Adults With Partial Seizures Already Receiving
1332 Treatment With Carbamazepine, Phenytoin, Phenobarbital, or Primidone as the Single
1333 Antiepileptic Drug: The effectiveness of monotherapy with LAMICTAL was established in a
1334 multicenter, double-blind clinical trial enrolling 156 adult outpatients with partial seizures. The
1335 patients experienced at least 4 simple partial, complex partial, and/or secondarily generalized
1336 seizures during each of 2 consecutive 4-week periods while receiving carbamazepine or
1337 phenytoin monotherapy during baseline. LAMICTAL (target dose of 500 mg/day) or valproate
1338 (1,000 mg/day) was added to either carbamazepine or phenytoin monotherapy over a 4-week
1339 period. Patients were then converted to monotherapy with LAMICTAL or valproate during the
1340 next 4 weeks, then continued on monotherapy for an additional 12-week period.

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1341 Study endpoints were completion of all weeks of study treatment or meeting an escape
1342 criterion. Criteria for escape relative to baseline were: (1) doubling of average monthly seizure
1343 count, (2) doubling of highest consecutive 2-day seizure frequency, (3) emergence of a new
1344 seizure type (defined as a seizure that did not occur during the 8-week baseline) that is more
1345 severe than seizure types that occur during study treatment, or (4) clinically significant
1346 prolongation of generalized tonic-clonic seizures. The primary efficacy variable was the
1347 proportion of patients in each treatment group who met escape criteria.

1348 The percentages of patients who met escape criteria were 42% (32/76) in the group
1349 receiving LAMICTAL and 69% (55/80) in the valproate group. The difference in the percentage
1350 of patients meeting escape criteria was statistically significant ($P = 0.0012$) in favor of
1351 LAMICTAL. No differences in efficacy based on age, sex, or race were detected.

1352 Patients in the control group were intentionally treated with a relatively low dose of
1353 valproate; as such, the sole objective of this study was to demonstrate the effectiveness and
1354 safety of monotherapy with LAMICTAL, and cannot be interpreted to imply the superiority of
1355 LAMICTAL to an adequate dose of valproate.

1356 Adjunctive Therapy With LAMICTAL in Adults With Partial Seizures: The
1357 effectiveness of LAMICTAL as adjunctive therapy (added to other AEDs) was established in 3
1358 multicenter, placebo-controlled, double-blind clinical trials in 355 adults with refractory partial
1359 seizures. The patients had a history of at least 4 partial seizures per month in spite of receiving
1360 one or more AEDs at therapeutic concentrations and, in 2 of the studies, were observed on their
1361 established AED regimen during baselines that varied between 8 to 12 weeks. In the third,
1362 patients were not observed in a prospective baseline. In patients continuing to have at least 4
1363 seizures per month during the baseline, LAMICTAL or placebo was then added to the existing
1364 therapy. In all 3 studies, change from baseline in seizure frequency was the primary measure of
1365 effectiveness. The results given below are for all partial seizures in the intent-to-treat population
1366 (all patients who received at least one dose of treatment) in each study, unless otherwise
1367 indicated. The median seizure frequency at baseline was 3 per week while the mean at baseline
1368 was 6.6 per week for all patients enrolled in efficacy studies.

1369 One study ($n = 216$) was a double-blind, placebo-controlled, parallel trial consisting of a
1370 24-week treatment period. Patients could not be on more than 2 other anticonvulsants and
1371 valproate was not allowed. Patients were randomized to receive placebo, a target dose of 300
1372 mg/day of LAMICTAL, or a target dose of 500 mg/day of LAMICTAL. The median reductions
1373 in the frequency of all partial seizures relative to baseline were 8% in patients receiving placebo,
1374 20% in patients receiving 300 mg/day of LAMICTAL, and 36% in patients receiving 500
1375 mg/day of LAMICTAL. The seizure frequency reduction was statistically significant in the 500-
1376 mg/day group compared with the placebo group, but not in the 300-mg/day group.

1377 A second study ($n = 98$) was a double-blind, placebo-controlled, randomized, crossover
1378 trial consisting of two 14-week treatment periods (the last 2 weeks of which consisted of dose
1379 tapering) separated by a 4-week washout period. Patients could not be on more than 2 other

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1380 anticonvulsants and valproate was not allowed. The target dose of LAMICTAL was 400 mg/day.
1381 When the first 12 weeks of the treatment periods were analyzed, the median change in seizure
1382 frequency was a 25% reduction on LAMICTAL compared with placebo ($P<0.001$).

1383 The third study ($n = 41$) was a double-blind, placebo-controlled, crossover trial consisting
1384 of two 12-week treatment periods separated by a 4-week washout period. Patients could not be
1385 on more than 2 other anticonvulsants. Thirteen patients were on concomitant valproate; these
1386 patients received 150 mg/day of LAMICTAL. The 28 other patients had a target dose of 300
1387 mg/day of LAMICTAL. The median change in seizure frequency was a 26% reduction on
1388 LAMICTAL compared with placebo ($P<0.01$).

1389 No differences in efficacy based on age, sex, or race, as measured by change in seizure
1390 frequency, were detected.

1391 Adjunctive Therapy With LAMICTAL in Pediatric Patients With Partial Seizures:

1392 The effectiveness of LAMICTAL as adjunctive therapy in pediatric patients with partial seizures
1393 was established in a multicenter, double-blind, placebo-controlled trial in 199 patients 2 to 16
1394 years of age ($n = 98$ on LAMICTAL, $n = 101$ on placebo). Following an 8-week baseline phase,
1395 patients were randomized to 18 weeks of treatment with LAMICTAL or placebo added to their
1396 current AED regimen of up to 2 drugs. Patients were dosed based on body weight and valproate
1397 use. Target doses were designed to approximate 5 mg/kg/day for patients taking valproate
1398 (maximum dose: 250 mg/day) and 15 mg/kg/day for the patients not taking valproate (maximum
1399 dose: 750 mg/day). The primary efficacy endpoint was percentage change from baseline in all
1400 partial seizures. For the intent-to-treat population, the median reduction of all partial seizures
1401 was 36% in patients treated with LAMICTAL and 7% on placebo, a difference that was
1402 statistically significant ($P<0.01$).

1403 Adjunctive Therapy With LAMICTAL in Pediatric and Adult Patients With Lennox-

1404 Gastaut Syndrome: The effectiveness of LAMICTAL as adjunctive therapy in patients with
1405 Lennox-Gastaut syndrome was established in a multicenter, double-blind, placebo-controlled
1406 trial in 169 patients 3 to 25 years of age ($n = 79$ on LAMICTAL, $n = 90$ on placebo). Following a
1407 4-week single-blind, placebo phase, patients were randomized to 16 weeks of treatment with
1408 LAMICTAL or placebo added to their current AED regimen of up to 3 drugs. Patients were
1409 dosed on a fixed-dose regimen based on body weight and valproate use. Target doses were
1410 designed to approximate 5 mg/kg/day for patients taking valproate (maximum dose: 200 mg/day)
1411 and 15 mg/kg/day for patients not taking valproate (maximum dose: 400 mg/day). The primary
1412 efficacy endpoint was percentage change from baseline in major motor seizures (atonic, tonic,
1413 major myoclonic, and tonic-clonic seizures). For the intent-to-treat population, the median
1414 reduction of major motor seizures was 32% in patients treated with LAMICTAL and 9% on
1415 placebo, a difference that was statistically significant ($P<0.05$). Drop attacks were significantly
1416 reduced by LAMICTAL (34%) compared with placebo (9%), as were tonic-clonic seizures (36%
1417 reduction versus 10% increase for LAMICTAL and placebo, respectively).

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1418 Adjunctive Therapy With LAMICTAL in Pediatric and Adult Patients With Primary
1419 Generalized Tonic-Clonic Seizures: The effectiveness of LAMICTAL as adjunctive therapy
1420 in patients with primary generalized tonic-clonic seizures was established in a multicenter,
1421 double-blind, placebo-controlled trial in 117 pediatric and adult patients ≥ 2 years ($n = 58$ on
1422 LAMICTAL, $n = 59$ on placebo). Patients with at least 3 primary generalized tonic-clonic
1423 seizures during an 8-week baseline phase were randomized to 19 to 24 weeks of treatment with
1424 LAMICTAL or placebo added to their current AED regimen of up to 2 drugs. Patients were
1425 dosed on a fixed-dose regimen, with target doses ranging from 3 mg/kg/day to 12 mg/kg/day for
1426 pediatric patients and from 200 mg/day to 400 mg/day for adult patients based on concomitant
1427 AED.

1428 The primary efficacy endpoint was percentage change from baseline in primary
1429 generalized tonic-clonic seizures. For the intent-to-treat population, the median percent reduction
1430 of primary generalized tonic-clonic seizures was 66% in patients treated with LAMICTAL and
1431 34% on placebo, a difference that was statistically significant ($P = 0.006$).

1432 **14.2 Bipolar Disorder**

1433 The effectiveness of LAMICTAL in the maintenance treatment of Bipolar I Disorder was
1434 established in 2 multicenter, double-blind, placebo-controlled studies in adult patients who met
1435 DSM-IV criteria for Bipolar I Disorder. Study 1 enrolled patients with a current or recent (within
1436 60 days) depressive episode as defined by DSM-IV and Study 2 included patients with a current
1437 or recent (within 60 days) episode of mania or hypomania as defined by DSM-IV. Both studies
1438 included a cohort of patients (30% of 404 patients in Study 1 and 28% of 171 patients in Study
1439 2) with rapid cycling Bipolar Disorder (4 to 6 episodes per year).

1440 In both studies, patients were titrated to a target dose of 200 mg of LAMICTAL, as add-
1441 on therapy or as monotherapy, with gradual withdrawal of any psychotropic medications during
1442 an 8- to 16-week open-label period. Overall 81% of 1,305 patients participating in the open-label
1443 period were receiving 1 or more other psychotropic medications, including benzodiazepines,
1444 selective serotonin reuptake inhibitors (SSRIs), atypical antipsychotics (including olanzapine),
1445 valproate, or lithium, during titration of LAMICTAL. Patients with a CGI-severity score of 3 or
1446 less maintained for at least 4 continuous weeks, including at least the final week on monotherapy
1447 with LAMICTAL, were randomized to a placebo-controlled, double-blind treatment period for
1448 up to 18 months. The primary endpoint was TIME (time to intervention for a mood episode or
1449 one that was emerging, time to discontinuation for either an adverse event that was judged to be
1450 related to Bipolar Disorder, or for lack of efficacy). The mood episode could be depression,
1451 mania, hypomania, or a mixed episode.

1452 In Study 1, patients received double-blind monotherapy with LAMICTAL 50 mg/day ($n =$
1453 50), LAMICTAL 200 mg/day ($n = 124$), LAMICTAL 400 mg/day ($n = 47$), or placebo ($n =$
1454 121). LAMICTAL (200- and 400-mg/day treatment groups combined) was superior to placebo in
1455 delaying the time to occurrence of a mood episode. Separate analyses of the 200- and 400-
1456 mg/day dose groups revealed no added benefit from the higher dose.

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1457 In Study 2, patients received double-blind monotherapy with LAMICTAL (100 to 400
1458 mg/day, n = 59), or placebo (n = 70). LAMICTAL was superior to placebo in delaying time to
1459 occurrence of a mood episode. The mean dose of LAMICTAL was about 211 mg/day.

1460 Although these studies were not designed to separately evaluate time to the occurrence of
1461 depression or mania, a combined analysis for the 2 studies revealed a statistically significant
1462 benefit for LAMICTAL over placebo in delaying the time to occurrence of both depression and
1463 mania, although the finding was more robust for depression.

1464 **16 HOW SUPPLIED/STORAGE AND HANDLING**

1465 **LAMICTAL (lamotrigine) Tablets**

1466 25 mg, white, scored, shield-shaped tablets debossed with “LAMICTAL” and “25”,
1467 bottles of 100 (NDC 0173-0633-02).

1468 Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled
1469 Room Temperature] in a dry place.

1470 100 mg, peach, scored, shield-shaped tablets debossed with “LAMICTAL” and “100”,
1471 bottles of 100 (NDC 0173-0642-55).

1472 150 mg, cream, scored, shield-shaped tablets debossed with “LAMICTAL” and “150”,
1473 bottles of 60 (NDC 0173-0643-60).

1474 200 mg, blue, scored, shield-shaped tablets debossed with “LAMICTAL” and “200”,
1475 bottles of 60 (NDC 0173-0644-60).

1476 Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled
1477 Room Temperature] in a dry place and protect from light.

1478

1479 **LAMICTAL (lamotrigine) Starter Kit for Patients Taking Valproate (Blue Kit)**

1480 25 mg, white, scored, shield-shaped tablets debossed with “LAMICTAL” and “25”,
1481 blisterpack of 35 tablets (NDC 0173-0633-10).

1482 Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled
1483 Room Temperature] in a dry place.

1484 **LAMICTAL (lamotrigine) Starter Kit for Patients Taking Carbamazepine, 1485 Phenytoin, Phenobarbital, or Primidone and Not Taking Valproate (Green Kit)**

1486 25 mg, white, scored, shield-shaped tablets debossed with “LAMICTAL” and “25” and
1487 100 mg, peach, scored, shield-shaped tablets debossed with “LAMICTAL” and “100”,
1488 blisterpack of 98 tablets (84/25-mg tablets and 14/100-mg tablets) (NDC 0173-0817-28).

1489 Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled
1490 Room Temperature] in a dry place and protect from light.

1491 **LAMICTAL (lamotrigine) Starter Kit for Patients Not Taking Carbamazepine, 1492 Phenytoin, Phenobarbital, Primidone, or Valproate (Orange Kit)**

1493 25 mg, white, scored, shield-shaped tablets debossed with “LAMICTAL” and “25” and
1494 100 mg, peach, scored, shield-shaped tablets debossed with “LAMICTAL” and “100”,
1495 blisterpack of 49 tablets (42/25-mg tablets and 7/100-mg tablets) (NDC 0173-0594-02).

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1496 Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled
1497 Room Temperature] in a dry place and protect from light.

1498

1499 **LAMICTAL (lamotrigine) Chewable Dispersible Tablets**

1500 2 mg, white to off-white, round tablets debossed with “LTG” over “2”, bottles of 30
1501 (NDC 0173-0699-00). ORDER DIRECTLY FROM GlaxoSmithKline 1-800-334-4153.

1502 5 mg, white to off-white, caplet-shaped tablets debossed with “GX CL2”, bottles of 100
1503 (NDC 0173-0526-00).

1504 25 mg, white, super elliptical-shaped tablets debossed with “GX CL5”, bottles of 100
1505 (NDC 0173-0527-00).

1506 Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled
1507 Room Temperature] in a dry place.

1508

1509 **LAMICTAL ODT (lamotrigine) Orally Disintegrating Tablets**

1510 25 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with “LMT”
1511 on one side and “25” on the other, Maintenance Packs of 30 (NDC 0173-0772-02).

1512 50 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with “LMT”
1513 on one side and “50” on the other, Maintenance Packs of 30 (NDC 0173-0774-02).

1514 100 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with
1515 “LAMICTAL” on one side and “100” on the other, Maintenance Packs of 30 (NDC 0173-0776-
1516 02).

1517 200 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with
1518 “LAMICTAL” on one side and “200” on the other, Maintenance Packs of 30 (NDC 0173-0777-
1519 02).

1520 Store between 20°C to 25°C (68°F to 77°F); with excursions permitted between 15°C and
1521 30°C (59°F and 86°F).

1522 **LAMICTAL ODT (lamotrigine) Patient Titration Kit for Patients Taking Valproate**
1523 **(Blue ODT Kit)**

1524 25 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with “LMT”
1525 on one side and “25” on the other, and 50 mg, white to off-white, round, flat-faced, radius edge,
1526 tablets debossed with “LMT” on one side and “50” on the other, blisterpack of 28 tablets
1527 (21/25-mg tablets and 7/50-mg tablets) (NDC 0173-0779-00).

1528 **LAMICTAL ODT (lamotrigine) Patient Titration Kit for Patients Taking**
1529 **Carbamazepine, Phenytoin, Phenobarbital, or Primidone and Not Taking Valproate**
1530 **(Green ODT Kit)**

1531 50 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with “LMT”
1532 on one side and “50” on the other, and 100 mg, white to off-white, round, flat-faced, radius edge,
1533 tablets debossed with “LAMICTAL” on one side and “100” on the other, blisterpack of 56
1534 tablets (42/50-mg tablets and 14/100-mg tablets) (NDC 0173-0780-00).

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1535 **LAMICTAL ODT (lamotrigine) Patient Titration Kit for Patients Not Taking**
1536 **Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate (Orange ODT Kit)**
1537 25 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with “LMT”
1538 on one side and “25” on the other, 50 mg, white to off-white, round, flat-faced, radius edge,
1539 tablets debossed with “LMT” on one side and “50” on the other, and 100 mg, white to off-white,
1540 round, flat-faced, radius edge, tablets debossed with “LAMICTAL” on one side and “100” on the
1541 other, blisterpack of 35 (14/25-mg tablets, 14/50-mg tablets, and 7/100-mg tablets) (NDC 0173-
1542 0778-00).

1543 Store between 20°C to 25°C (68°F to 77°F); with excursions permitted between 15°C and
1544 30°C (59°F and 86°F).

1545 **Blisterpacks:** If the product is dispensed in a blisterpack, the patient should be advised to
1546 examine the blisterpack before use and not use if blisters are torn, broken, or missing.

1547 **17 PATIENT COUNSELING INFORMATION**

1548 *See FDA-approved patient labeling (Medication Guide).*

1549 **17.1 Rash**

1550 Prior to initiation of treatment with LAMICTAL, the patient should be instructed that a
1551 rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy) may herald a
1552 serious medical event and that the patient should report any such occurrence to a physician
1553 immediately.

1554 **17.2 Multiorgan Hypersensitivity Reactions, Blood Dyscrasias, and Organ 1555 Failure**

1556 Patients should be instructed that multiorgan hypersensitivity reactions and acute
1557 multiorgan failure may occur with LAMICTAL. Isolated organ failure or isolated blood
1558 dyscrasias without evidence of multiorgan hypersensitivity may also occur. Patients should
1559 contact their physician immediately if they experience any signs or symptoms of these conditions
1560 [*see Warnings and Precautions (5.2, 5.3)*].

1561 **17.3 Suicidal Thinking and Behavior**

1562 Patients, their caregivers, and families should be counseled that AEDs, including
1563 LAMICTAL, may increase the risk of suicidal thoughts and behavior and should be advised of
1564 the need to be alert for the emergence or worsening of symptoms of depression, any unusual
1565 changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about
1566 self-harm. Behaviors of concern should be reported immediately to healthcare providers.

1567 **17.4 Worsening of Seizures**

1568 Patients should be advised to notify their physician if worsening of seizure control
1569 occurs.

1570 **17.5 Central Nervous System Adverse Effects**

1571 Patients should be advised that LAMICTAL may cause dizziness, somnolence, and other
1572 symptoms and signs of CNS depression. Accordingly, they should be advised neither to drive a

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1573 car nor to operate other complex machinery until they have gained sufficient experience on
1574 LAMICTAL to gauge whether or not it adversely affects their mental and/or motor performance.

1575 **17.6 Pregnancy and Nursing**

1576 Patients should be advised to notify their physicians if they become pregnant or intend to
1577 become pregnant during therapy. Patients should be advised to notify their physicians if they
1578 intend to breastfeed or are breastfeeding an infant.

1579 Patients should also be encouraged to enroll in the NAAED Pregnancy Registry if they
1580 become pregnant. This registry is collecting information about the safety of antiepileptic drugs
1581 during pregnancy. To enroll, patients can call the toll-free number 1-888-233-2334 [*see Use in*
1582 *Specific Populations (8.1)*].

1583 Patients who intend to breastfeed should be informed that LAMICTAL is present in
1584 breast milk and that they should monitor their child for potential adverse effects of this drug.
1585 Benefits and risks of continuing breastfeeding should be discussed with the patient.

1586 **17.7 Oral Contraceptive Use**

1587 Women should be advised to notify their physician if they plan to start or stop use of oral
1588 contraceptives or other female hormonal preparations. Starting estrogen-containing oral
1589 contraceptives may significantly decrease lamotrigine plasma levels and stopping estrogen-
1590 containing oral contraceptives (including the “pill-free” week) may significantly increase
1591 lamotrigine plasma levels [*see Warnings and Precautions (5.8), Clinical Pharmacology (12.3)*].
1592 Women should also be advised to promptly notify their physician if they experience adverse
1593 reactions or changes in menstrual pattern (e.g., break-through bleeding) while receiving
1594 LAMICTAL in combination with these medications.

1595 **17.8 Discontinuing LAMICTAL**

1596 Patients should be advised to notify their physician if they stop taking LAMICTAL for
1597 any reason and not to resume LAMICTAL without consulting their physician.

1598 **17.9 Aseptic Meningitis**

1599 Patients should be advised that LAMICTAL may cause aseptic meningitis. Patients
1600 should be advised to notify their physician immediately if they develop signs and symptoms of
1601 meningitis such as headache, fever, nausea, vomiting, stiff neck, rash, abnormal sensitivity to
1602 light, myalgia, chills, confusion, or drowsiness while taking LAMICTAL.

1603 **17.10 Potential Medication Errors**

1604 Medication errors involving LAMICTAL have occurred. In particular the names
1605 LAMICTAL or lamotrigine can be confused with the names of other commonly used
1606 medications. Medication errors may also occur between the different formulations of
1607 LAMICTAL. To reduce the potential of medication errors, write and say LAMICTAL clearly.
1608 Depictions of the LAMICTAL Tablets, Chewable Dispersible Tablets, and Orally Disintegrating
1609 Tablets can be found in the Medication Guide that accompanies the product to highlight the
1610 distinctive markings, colors, and shapes that serve to identify the different presentations of the
1611 drug and thus may help reduce the risk of medication errors. **To avoid a medication error of**

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1612 **using the wrong drug or formulation, patients should be strongly advised to visually**
1613 **inspect their tablets to verify that they are LAMICTAL, as well as the correct formulation**
1614 **of LAMICTAL, each time they fill their prescription** [*see Dosage Forms and Strengths (3.1,*
1615 *3.2, 3.3), How Supplied/Storage and Handling (16)].*

1616

1617 LAMICTAL is a registered trademark of GlaxoSmithKline.

1618 Microcaps and AdvaTab are registered trademarks of Eurand, Inc.

1619

1620



1621

1622 GlaxoSmithKline

1623 Research Triangle Park, NC 27709

1624

1625 LAMICTAL Tablets and Chewable Dispersible Tablets are manufactured by

1626 DSM Pharmaceuticals, Inc., Greenville, NC 27834 or

1627 GlaxoSmithKline, Research Triangle Park, NC 27709

1628

1629 LAMICTAL Orally Disintegrating Tablets are manufactured by

1630 Eurand, Inc., Vandalia, OH 45377

1631

1632

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1634

1635 Month Year

1636 LMT:xPI

1637

1638

MEDICATION GUIDE

1639

1640 **LAMICTAL[®] (la-MIK-tal) (lamotrigine) Tablets and Chewable Dispersible Tablets**

1641 **LAMICTAL[®] ODT[™] (lamotrigine) Orally Disintegrating Tablets**

1642

1643 Read this Medication Guide before you start taking LAMICTAL and each time you get a refill.

1644 There may be new information. This information does not take the place of talking with your

1645 healthcare provider about your medical condition or treatment. If you have questions about

1646 LAMICTAL, ask your healthcare provider or pharmacist.

1647

1648 **What is the most important information I should know about LAMICTAL?**

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1649 **1. LAMICTAL may cause a serious skin rash that may cause you to be hospitalized or to**
1650 **stop LAMICTAL; it may rarely cause death.**

1651 There is no way to tell if a mild rash will develop into a more serious reaction. These serious
1652 skin reactions are more likely to happen when you begin taking LAMICTAL, within the first
1653 2 to 8 weeks of treatment. But it can happen in people who have taken LAMICTAL for any
1654 period of time. Children between 2 to 16 years of age have a higher chance of getting this
1655 serious skin reaction while taking LAMICTAL.

1656 The risk of getting a rash is higher if you:

- 1657 • take LAMICTAL while taking valproate [DEPAKENE (valproic acid) or DEPAKOTE
- 1658 (divalproex sodium)].
- 1659 • take a higher starting dose of LAMICTAL than your healthcare provider prescribed
- 1660 • increase your dose of LAMICTAL faster than prescribed.

1661 **LAMICTAL can also cause other types of allergic reactions or serious problems which**
1662 **may affect organs and other parts of your body like the liver or blood cells. You may or**
1663 **may not have a rash with these types of reactions.**

1664 **Call your healthcare provider right away if you have any of the following:**

- 1665 • a skin rash
- 1666 • hives
- 1667 • fever
- 1668 • swollen lymph glands
- 1669 • painful sores in the mouth or around your eyes
- 1670 • swelling of your lips or tongue
- 1671 • yellowing of your skin or eyes
- 1672 • unusual bruising or bleeding
- 1673 • severe fatigue or weakness
- 1674 • severe muscle pain
- 1675 • frequent infections

1676 These symptoms may be the first signs of a serious reaction. A healthcare provider should
1677 examine you to decide if you should continue taking LAMICTAL.

1678 **2. Like other antiepileptic drugs, LAMICTAL may cause suicidal thoughts or actions in a**
1679 **very small number of people, about 1 in 500.**

1680 **Call a healthcare provider right away if you have any of these symptoms, especially if**
1681 **they are new, worse, or worry you:**

- 1682 • thoughts about suicide or dying
- 1683 • attempt to commit suicide
- 1684 • new or worse depression
- 1685 • new or worse anxiety

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- 1686 • feeling agitated or restless
- 1687 • panic attacks
- 1688 • trouble sleeping (insomnia)
- 1689 • new or worse irritability
- 1690 • acting aggressive, being angry, or violent
- 1691 • acting on dangerous impulses
- 1692 • an extreme increase in activity and talking (mania)
- 1693 • other unusual changes in behavior or mood
- 1694 **Do not stop LAMICTAL without first talking to a healthcare provider.**
- 1695 • Stopping LAMICTAL suddenly can cause serious problems.
- 1696 • Suicidal thoughts or actions can be caused by things other than medicines. If you have
- 1697 suicidal thoughts or actions, your healthcare provider may check for other causes.
- 1698 **How can I watch for early symptoms of suicidal thoughts and actions?**
- 1699 • Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or
- 1700 feelings.
- 1701 • Keep all follow-up visits with your healthcare provider as scheduled.
- 1702 • Call your healthcare provider between visits as needed, especially if you are worried
- 1703 about symptoms.
- 1704 **3. LAMICTAL may rarely cause aseptic meningitis, a serious inflammation of the**
- 1705 **protective membrane that covers the brain and spinal cord.**
- 1706 **Call your healthcare provider right away if you have any of the following symptoms:**
- 1707 • Headache
- 1708 • Fever
- 1709 • Nausea
- 1710 • Vomiting
- 1711 • Stiff neck
- 1712 • Rash
- 1713 • Unusual sensitivity to light
- 1714 • Muscle pains
- 1715 • Chills
- 1716 • Confusion
- 1717 • Drowsiness
- 1718 Meningitis has many causes other than LAMICTAL, which your doctor would check for if
- 1719 you developed meningitis while taking LAMICTAL.
- 1720 **LAMICTAL can have other serious side effects.** For more information ask your healthcare
- 1721 provider or pharmacist. Tell your healthcare provider if you have any side effect that bothers

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1722 you. Be sure to read the section below entitled “What are the possible side effects of
1723 LAMICTAL?”





1724 **4. Patients prescribed LAMICTAL have sometimes been given the wrong medicine**
1725 **because many medicines have names similar to LAMICTAL, so always check that you**
1726 **receive LAMICTAL.**

1727 Taking the wrong medication can cause serious health problems. When your healthcare
1728 provider gives you a prescription for LAMICTAL:




- 1729 • Make sure you can read it clearly.
- 1730 • Talk to your pharmacist to check that you are given the correct medicine.
- 1731 • Each time you fill your prescription, check the tablets you receive against the pictures of
1732 the tablets below.

1733 These pictures show the distinct wording, colors, and shapes of the tablets that help to
1734 identify the right strength of LAMICTAL Tablets, Chewable Dispersible Tablets, and
1735 Orally Disintegrating Tablets. Immediately call your pharmacist if you receive a
1736 LAMICTAL tablet that does not look like one of the tablets shown below, as you may
1737 have received the wrong medication.


1738 **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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1739 **LAMICTAL (lamotrigine) Chewable Dispersible Tablets**

 2 mg, white Imprinted with LTG 2	 5 mg, white Imprinted with GX CL2	 25 mg, white Imprinted with GX CL5
--	---	--

1740 **LAMICTAL ODT (lamotrigine) Orally Disintegrating Tablets**

 25 mg, white to off-white	 50 mg, white to off-white	 100 mg, white to off-white	 200 mg, white to off-white
---	---	---	--

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Imprinted with LMT on one side 25 on the other	Imprinted with LMT on one side 50 on the other	Imprinted with LAMICTAL on one side 100 on the other	Imprinted with LAMICTAL on one side 200 on the other
---	---	---	---

1741

1742 **What is LAMICTAL?**

1743 LAMICTAL is a prescription medicine used:

- 1744 1. together with other medicines to treat certain types of seizures (partial seizures, primary
1745 generalized tonic-clonic seizures, generalized seizures of Lennox-Gastaut syndrome) in
1746 people 2 years or older.
- 1747 2. alone when changing from other medicines used to treat partial seizures in people 16 years or
1748 older.
- 1749 3. for the long-term treatment of Bipolar I Disorder to lengthen the time between mood
1750 episodes in people 18 years or older who have been treated for mood episodes with other
1751 medicine.

1752 It is not known if LAMICTAL is safe or effective in children or teenagers under the age of 18
1753 with mood disorders such as bipolar disorder or depression.

1754 It is not known if LAMICTAL is safe or effective when used alone as the first treatment of
1755 seizures in adults.

1756

1757 **Who should not take LAMICTAL?**

1758 You should not take LAMICTAL if you have had an allergic reaction to lamotrigine or to any of
1759 the inactive ingredients in LAMICTAL. See the end of this leaflet for a complete list of
1760 ingredients in LAMICTAL.

1761

1762 **What should I tell my healthcare provider before taking LAMICTAL?**

1763 Before taking LAMICTAL, tell your healthcare provider about all of your medical conditions,
1764 including if you:

- 1765 • have had a rash or allergic reaction to another antiseizure medicine.
- 1766 • have or have had depression, mood problems or suicidal thoughts or behavior.
- 1767 • are taking oral contraceptives (birth control pills) or other female hormonal medicines. Do
1768 not start or stop taking birth control pills or other female hormonal medicine until you have
1769 talked with your healthcare provider. Tell your healthcare provider if you have any changes
1770 in your menstrual pattern such as breakthrough bleeding. Stopping or starting these
1771 medicines may cause side effects (such as dizziness, lack of coordination, or double vision)
1772 or lessen how well LAMICTAL works.

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- 1773 • are pregnant or plan to become pregnant. It is not known if LAMICTAL will harm your
1774 unborn baby. If you become pregnant while taking LAMICTAL, talk to your healthcare
1775 provider about registering with the North American Antiepileptic Drug Pregnancy Registry.
1776 You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to
1777 collect information about the safety of antiepileptic drugs during pregnancy.
- 1778 • are breastfeeding. LAMICTAL passes into breast milk and may cause side effects in a
1779 breastfed baby. If you breastfeed while taking LAMICTAL, watch your baby closely for
1780 trouble breathing, episodes of temporarily stopping breathing, sleepiness, or poor sucking.
1781 Call your baby's healthcare provider right away if you see any of these problems. Talk to
1782 your healthcare provider about the best way to feed your baby if you take LAMICTAL.
- 1783 Tell your healthcare provider about all the medicines you take or if you are planning to take a
1784 new medicine, including prescription and non-prescription medicines, vitamins, and herbal
1785 supplements. Using LAMICTAL with certain other medicines can affect each other, causing side
1786 effects.

1787
1788

How should I take LAMICTAL?

- 1789 • Take LAMICTAL exactly as prescribed.
- 1790 • Your healthcare provider may change your dose. Do not change your dose without talking to
1791 your healthcare provider.
- 1792 • Do not stop taking LAMICTAL without talking to your healthcare provider. Stopping
1793 LAMICTAL suddenly may cause serious problems. For example, if you have epilepsy and
1794 you stop taking LAMICTAL suddenly, you may get seizures that do not stop. Talk with your
1795 healthcare provider about how to stop LAMICTAL slowly.
- 1796 • If you miss a dose of LAMICTAL, take it as soon as you remember. If it is almost time for
1797 your next dose, just skip the missed dose. Take the next dose at your regular time. **Do not**
1798 **take two doses at the same time.**
- 1799 • You may not feel the full effect of LAMICTAL for several weeks.
- 1800 • If you have epilepsy, tell your healthcare provider if your seizures get worse or if you have
1801 any new types of seizures.
- 1802 • Swallow LAMICTAL tablets whole.
- 1803 • If you have trouble swallowing LAMICTAL Tablets, there may be another form of
1804 LAMICTAL you can take.
- 1805 • LAMICTAL ODT should be placed on the tongue and moved around the mouth. The tablet
1806 will rapidly disintegrate, can be swallowed with or without water, and can be taken with or
1807 without food.
- 1808 • LAMICTAL Chewable Dispersible tablets may be swallowed whole, chewed, or mixed in
1809 water or diluted fruit juice. If the tablets are chewed, drink a small amount of water or diluted
1810 fruit juice to help in swallowing. To break up LAMICTAL Chewable Dispersible tablets, add
1811 the tablets to a small amount of liquid (1 teaspoon, or enough to cover the medicine) in a

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1812 glass or spoon. Wait at least 1 minute or until the tablets are completely broken up, mix the
1813 solution together and take the whole amount right away.
1814 • If you receive LAMICTAL in a blisterpack, examine the blisterpack before use. Do not use if
1815 blisters are torn, broken, or missing.

1816
1817 **What should I avoid while taking LAMICTAL?**

1818 • Do not drive a car or operate complex, hazardous machinery until you know how
1819 LAMICTAL affects you.

1820
1821 **What are possible side effects of LAMICTAL?**

1822 • See “What is the most important information I should know about LAMICTAL?”

1823 Common side effects of LAMICTAL include:

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

1824 Tell your healthcare provider about any side effect that bothers you or that does not go away.

1825 These are not all the possible side effects of LAMICTAL. For more information, ask your
1826 healthcare provider or pharmacist.

1827 Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-
1828 800-FDA-1088.

1829
1830 **How should I store LAMICTAL?**

1831 • Store LAMICTAL at room temperature between 68°F to 77°F (20°C to 25°C).
1832 • **Keep LAMICTAL and all medicines out of the reach of children.**

1833
1834 **General information about LAMICTAL**

1835 Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.
1836 Do not use LAMICTAL for a condition for which it was not prescribed. Do not give
1837 LAMICTAL to other people, even if they have the same symptoms you have. It may harm them.

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1838 This Medication Guide summarizes the most important information about LAMICTAL. If you
1839 would like more information, talk with your healthcare provider. You can ask your healthcare
1840 provider or pharmacist for information about LAMICTAL that is written for healthcare
1841 professionals.

1842 For more information, go to www.lamictal.com or call 1-888-825-5249.

1843

1844 **What are the ingredients in LAMICTAL?**

1845 **LAMICTAL Tablets**

1846 Active ingredient: lamotrigine.

1847 Inactive ingredients: lactose; magnesium stearate, microcrystalline cellulose, povidone, sodium
1848 starch glycolate, FD&C Yellow No. 6 Lake (100-mg tablet only), ferric oxide, yellow (150-mg
1849 tablet only), and FD&C Blue No. 2 Lake (200-mg tablet only).

1850 **LAMICTAL Chewable Dispersible Tablets**

1851 Active ingredient: lamotrigine.

1852 Inactive ingredients: blackcurrant flavor, calcium carbonate, low-substituted
1853 hydroxypropylcellulose, magnesium aluminum silicate, magnesium stearate, povidone, saccharin
1854 sodium, and sodium starch glycolate.

1855 **LAMICTAL ODT Orally Disintegrating Tablets**

1856 Active ingredient: lamotrigine.

1857 Inactive ingredients: artificial cherry flavor, crospovidone, ethylcellulose, magnesium stearate,
1858 mannitol, polyethylene, and sucralose.

1859

1860 **This Medication Guide has been approved by the U.S. Food and Drug Administration.**

1861

1862 LAMICTAL is a registered trademark of GlaxoSmithKline.

1863 DEPAKENE and DEPAKOTE are registered trademarks of Abbott Laboratories.

1864

1865



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1867 GlaxoSmithKline

1868 Research Triangle Park, NC 27709

1869

1870 LAMICTAL Tablets and Chewable Dispersible Tablets are manufactured by

1871 DSM Pharmaceuticals, Inc.,

1872 Greenville, NC 27834 or

1873 GlaxoSmithKline

NDA 020241/S-050
NDA 020764/ S-043
NDA 022251/S-013
FDA Approved Labeling Text dated 7/23/2012
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1874 Research Triangle Park, NC 27709
1875
1876 LAMICTAL Orally Disintegrating Tablets are manufactured by
1877 Eurand, Inc., Vandalia, OH 45377
1878
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1880
1881 Month Year
1882 LMT:xMG