

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

LAMICTAL XR (lamotrigine) Extended-Release Tablets
Initial U.S. Approval: 1994

WARNING: SERIOUS SKIN RASHES

See full prescribing information for complete boxed warning.

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

- coadministration with valproate
- exceeding recommended initial dose of LAMICTAL XR
- exceeding recommended dose escalation for LAMICTAL XR.

Benign rashes are also caused by lamotrigine; however, it is not possible to predict which rashes will prove to be serious or life threatening.

LAMICTAL XR should be discontinued at the first sign of rash, unless the rash is clearly not drug related. (5.1)

RECENT MAJOR CHANGES

Indications and Usage, Monotherapy (1.2)	April 2011
Dosage and Administration, Conversion from Adjunctive Therapy to Monotherapy (2.3)	April 2011
Warnings and Precautions, Aseptic Meningitis (5.6)	October 2010

INDICATIONS AND USAGE

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

- adjunctive therapy for primary generalized tonic-clonic (PGTC) seizures and partial onset seizures with or without secondary generalization in patients ≥ 13 years of age. (1.1)
- conversion to monotherapy in patients ≥ 13 years of age with partial seizures who are receiving treatment with a single AED. (1.2)
- Limitation of use: Safety and effectiveness in patients less than 13 years of age have not been established. (1.3)

DOSAGE AND ADMINISTRATION

- Do not exceed the recommended initial dosage and subsequent dose escalation. (2.1)
- Initiation of adjunctive therapy and conversion to monotherapy requires slow titration dependent on concomitant AEDs; the prescriber must refer to the appropriate algorithm in Dosage and Administration (2.2, 2.3)
 - Adjunct therapy target therapeutic dose range is 200 to 600 mg daily and is dependent on concomitant AEDs. (2.2)
 - Conversion to monotherapy: Target therapeutic dosage range is 250 to 300 mg daily. (2.3)
- Conversion from immediate-release lamotrigine to LAMICTAL XR: The initial dose of LAMICTAL XR should match the total daily dose of the immediate-release lamotrigine. Patients should be closely monitored for seizure control after conversion. (2.4)
- Do not restart LAMICTAL XR in patients who discontinued due to rash unless the potential benefits clearly outweigh the risks. (2.1, 5.1)
- Adjustments to maintenance doses are likely in patients starting or stopping estrogen-containing oral contraceptives. (2.1, 5.8)
- Discontinuation: Taper over a period of at least 2 weeks (approximately 50% dose reduction per week). (2.1, 5.9)

DOSAGE FORMS AND STRENGTHS
Extended-release tablets: 25 mg, 50 mg, 100 mg, 200 mg, and 300 mg. (3.1, 16)

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

- WARNINGS AND PRECAUTIONS**
- Life-threatening serious rash and/or rash-related death: Discontinue at the first sign of rash, unless the rash is clearly not drug related. (Boxed Warning, 5.1)
 - Fatal or life-threatening hypersensitivity reaction: Monitor for early signs of hypersensitivity (e.g., fever, lymphadenopathy), which may present without rash; if signs present, patient should be evaluated immediately. Discontinue LAMICTAL XR if alternate etiology is not found. (5.2)
 - Acute multiorgan failure has resulted (some cases fatal). Monitor for hypersensitivity signs with multiple organ dysfunction. (5.3)
 - Blood dyscrasias (e.g., neutropenia, thrombocytopenia, pancytopenia): May occur, either with or without an associated hypersensitivity syndrome. Monitor for signs of anemia, unexpected infection, or bleeding. (5.4)
 - Suicidal behavior and ideation: Monitor for suicidal thoughts or behaviors. (5.5)
 - Aseptic meningitis: Monitor for signs of meningitis. (5.6)
 - Medication errors due to product name confusion: Strongly advise patients to visually inspect tablets to verify the received drug is correct. (3.2, 5.7, 16, 17.10)

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

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

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

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2011

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

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2 **FULL PRESCRIBING INFORMATION**

3 **WARNING: SERIOUS SKIN RASHES**

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

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

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

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

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

37 **1 INDICATIONS AND USAGE**

38 **1.1 Adjunctive Therapy**

39 LAMICTAL XR is indicated as adjunctive therapy for primary generalized tonic-clonic
40 (PGTC) seizures and partial onset seizures with or without secondary generalization in patients
41 ≥ 13 years of age.

42 **1.2 Monotherapy**

43 LAMICTAL XR is indicated for conversion to monotherapy in patients ≥ 13 years of age
44 with partial seizures who are receiving treatment with a single antiepileptic drug (AED).

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

48 **1.3 Limitation of Use**

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

51 **2 DOSAGE AND ADMINISTRATION**

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

54 **2.1 General Dosing Considerations**

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

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

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

70 It is recommended that LAMICTAL XR not be restarted in patients who discontinued
71 due to rash associated with prior treatment with lamotrigine, unless the potential benefits clearly
72 outweigh the risks. If the decision is made to restart a patient who has discontinued LAMICTAL
73 XR, the need to restart with the initial dosing recommendations should be assessed. The greater
74 the interval of time since the previous dose, the greater consideration should be given to
75 restarting with the initial dosing recommendations. If a patient has discontinued lamotrigine for a

76 period of more than 5 half-lives, it is recommended that initial dosing recommendations and
77 guidelines be followed. The half-life of lamotrigine is affected by other concomitant medications
78 [see *Clinical Pharmacology (12.3)*].

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

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

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

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

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

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

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

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

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

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

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

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

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

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

165 **2.2 Adjunctive Therapy for Primary Generalized Tonic-Clonic and Partial Onset**
 166 **Seizures**

167 This section provides specific dosing recommendations for patients ≥ 13 years of age.
 168 Specific dosing recommendations are provided depending upon concomitant AED or other
 169 concomitant medications.

170

171 **Table 1. Escalation Regimen for LAMICTAL XR in Patients ≥ 13 Years of Age**

	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 every day	50 mg every day
Weeks 3 and 4	25 mg every day	50 mg every day	100 mg every day
Week 5	50 mg every day	100 mg every day	200 mg every day
Week 6	100 mg every day	150 mg every day	300 mg every day
Week 7	150 mg every day	200 mg every day	400 mg every day
Maintenance range (week 8 and onward)	200 to 250 mg every day ^c	300 to 400 mg every day ^c	400 to 600 mg every day ^c

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

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

181 ^c Dose increases at week 8 or later should not exceed 100 mg daily at weekly intervals.

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2.3 Conversion From Adjunctive Therapy to Monotherapy

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

The recommended maintenance dosage range of LAMICTAL XR as monotherapy is 250 to 300 mg given once daily.

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

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

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

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

Table 2. Conversion From Adjunctive Therapy With Valproate to Monotherapy With LAMICTAL XR in Patients ≥ 13 Years of Age With Epilepsy

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

Conversion From Adjunctive Therapy With Antiepileptic Drugs Other Than Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate to Monotherapy With LAMICTAL XR: After achieving a dosage of 250 to 300 mg/day of LAMICTAL XR using the guidelines in Table 1, the concomitant AED should be withdrawn by 20% decrements each week over a 4-week period. No adjustment to the monotherapy dose of LAMICTAL XR is needed.

2.4 Conversion From Immediate-Release Lamotrigine Tablets to LAMICTAL XR

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

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

221 **3 DOSAGE FORMS AND STRENGTHS**

222 **3.1 Extended-Release Tablets**

223 25 mg, yellow with white center, round, biconvex, film-coated tablets printed with
224 “LAMICTAL” and “XR 25.”

225 50 mg, green with white center, round, biconvex, film-coated tablets printed with
226 “LAMICTAL” and “XR 50.”

227 100 mg, orange with white center, round, biconvex, film-coated tablets printed with
228 “LAMICTAL” and “XR 100.”

229 200 mg, blue with white center, round, biconvex, film-coated tablets printed with
230 “LAMICTAL” and “XR 200.”

231 300 mg, gray with white center, caplet-shaped, film-coated tablets printed with
232 “LAMICTAL” and “XR 300.”

233 **3.2 Potential Medication Errors**

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

238 **4 CONTRAINDICATIONS**

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

242 **5 WARNINGS AND PRECAUTIONS**

243 **5.1 Serious Skin Rashes**

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

248 Pediatric Population: The incidence of serious rash associated with hospitalization and
249 discontinuation of immediate-release lamotrigine in a prospectively followed cohort of pediatric

250 patients (aged 2 to 16 years) with epilepsy receiving adjunctive therapy with immediate-release
251 lamotrigine was approximately 0.8% (16 of 1,983). When 14 of these cases were reviewed by 3
252 expert dermatologists, there was considerable disagreement as to their proper classification. To
253 illustrate, one dermatologist considered none of the cases to be Stevens-Johnson syndrome;
254 another assigned 7 of the 14 to this diagnosis. There was 1 rash-related death in this 1,983-
255 patient cohort. Additionally, there have been rare cases of toxic epidermal necrolysis with and
256 without permanent sequelae and/or death in US and foreign postmarketing experience.

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

261 LAMICTAL XR is not approved in patients less than 13 years of age.

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

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

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

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

280 **5.2 Hypersensitivity Reactions**

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

288 **Prior to initiation of treatment with LAMICTAL XR, the patient should be**
289 **instructed that a rash or other signs or symptoms of hypersensitivity (e.g., fever,**

290 **lymphadenopathy) may herald a serious medical event and that the patient should report**
291 **any such occurrence to a physician immediately.**

292 **5.3 Acute Multiorgan Failure**

293 Multiorgan failure, which in some cases has been fatal or irreversible, has been observed
294 in patients receiving immediate-release lamotrigine. Fatalities associated with multiorgan failure
295 and various degrees of hepatic failure have been reported in 2 of 3,796 adult patients and 4 of
296 2,435 pediatric patients who received immediate-release lamotrigine in epilepsy clinical trials.
297 Rare fatalities from multiorgan failure have been reported in compassionate plea and
298 postmarketing use. The majority of these deaths occurred in association with other serious
299 medical events, including status epilepticus and overwhelming sepsis, and hantavirus, making it
300 difficult to identify the initial cause.

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

308 **5.4 Blood Dyscrasias**

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

313 **5.5 Suicidal Behavior and Ideation**

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

318 Pooled analyses of 199 placebo-controlled clinical trials (monotherapy and adjunctive
319 therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had
320 approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or
321 behavior compared to patients randomized to placebo. In these trials, which had a median
322 treatment duration of 12 weeks, the estimated incidence of suicidal behavior or ideation among
323 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated
324 patients, representing an increase of approximately 1 case of suicidal thinking or behavior for
325 every 530 patients treated. There were 4 suicides in drug-treated patients in the trials and none in
326 placebo-treated patients, but the number of events is too small to allow any conclusion about
327 drug effect on suicide.

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

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

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

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

337

338 **Table 3. Risk by Indication for Antiepileptic Drugs in the Pooled Analysis**

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

339

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

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

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

354 **5.6 Aseptic Meningitis**

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

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

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

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

376 **5.7 Potential Medication Errors**

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

393 **5.8 Concomitant Use With Oral Contraceptives**

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

401 **5.9 Withdrawal Seizures**

402 As with other AEDs, LAMICTAL XR should not be abruptly discontinued. In patients
403 with epilepsy there is a possibility of increasing seizure frequency. Unless safety concerns
404 require a more rapid withdrawal, the dose of LAMICTAL XR should be tapered over a period of
405 at least 2 weeks (approximately 50% reduction per week) [*see Dosage and Administration*
406 (2.1)].

407 **5.10 Status Epilepticus**

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

414 **5.11 Sudden Unexplained Death in Epilepsy**

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

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

433 **5.12 Addition of LAMICTAL XR to a Multidrug Regimen That Includes Valproate**

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

437 **5.13 Binding in the Eye and Other Melanin-Containing Tissues**

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

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

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

447 **5.14 Laboratory Tests**

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

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

459 **6 ADVERSE REACTIONS**

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

- 462 • Serious skin rashes [see *Warnings and Precautions (5.1)*]
- 463 • Hypersensitivity reactions [see *Warnings and Precautions (5.2)*]
- 464 • Acute multiorgan failure [see *Warnings and Precautions (5.3)*]
- 465 • Blood dyscrasias [see *Warnings and Precautions (5.4)*]
- 466 • Suicidal behavior and ideation [see *Warnings and Precautions (5.5)*]
- 467 • Aseptic meningitis [see *Warnings and Precautions (5.6)*]
- 468 • Withdrawal seizures [see *Warnings and Precautions (5.9)*]
- 469 • Status epilepticus [see *Warnings and Precautions (5.10)*]
- 470 • Sudden unexplained death in epilepsy [see *Warnings and Precautions (5.11)*]

471 **6.1 Clinical Trial Experience With LAMICTAL XR for Treatment of Primary** 472 **Generalized Tonic-Clonic and Partial Onset Seizures**

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

477 LAMICTAL XR has been evaluated for safety in patients ≥ 13 years of age with PGTC
478 and partial onset seizures. The most commonly observed adverse reactions in these 2 double-
479 blind, placebo-controlled trials of adjunctive therapy with LAMICTAL XR were, in order of

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

482 In these 2 trials, adverse reactions led to withdrawal of 4 (2%) patients in the group
 483 receiving placebo and 10 (5%) patients in the group receiving LAMICTAL XR. Dizziness was
 484 the most common reason for withdrawal in the group receiving LAMICTAL XR (5 patients
 485 [3%]). The next most common adverse reactions leading to withdrawal in 2 patients each (1%)
 486 were rash, headache, nausea, and nystagmus.

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

490 **Table 4. Adverse Reaction Incidence in Double-Blind, Placebo-Controlled Adjunctive**
 491 **Trials of Patients With Epilepsy (Adverse Reactions $\geq 2\%$ of Patients Treated With**
 492 **LAMICTAL XR and Numerically More Frequent Than in the Placebo Group)**

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

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

493 Note: In these trials the incidence of nonserious rash was 2% for LAMICTAL XR and 3% for
 494 placebo. In clinical trials evaluating immediate-release lamotrigine, the rate of serious rash was
 495 0.3% in adults on adjunctive therapy for epilepsy [see *Boxed Warning*].
 496

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

500 The incidence for many adverse reactions caused by treatment with LAMICTAL XR was
 501 increased relative to placebo (i.e., treatment difference between LAMICTAL XR and placebo
 502 $\geq 2\%$) in either the titration or maintenance phases of the study. During the titration phase, an
 503 increased incidence (shown in descending order of % treatment difference) was observed for
 504 diarrhea, nausea, vomiting, somnolence, vertigo, myalgia, hot flush, and anxiety. During the
 505 maintenance phase, an increased incidence was observed for dizziness, tremor, and diplopia.
 506 Some adverse reactions developing in the titration phase were notable for persisting (>7 days)
 507 into the maintenance phase. These “persistent” adverse reactions included somnolence and
 508 dizziness.

509 There were inadequate data to evaluate the effect of dose and/or concentration on the
 510 incidence of adverse reactions because, although patients were randomized to different target
 511 doses based upon concomitant AED, the plasma exposure was expected to be generally similar
 512 among all patients receiving different doses. However, in a randomized, parallel study
 513 comparing placebo and 300 and 500 mg/day of immediate-release lamotrigine, the incidence of
 514 the most common adverse reactions ($\geq 5\%$) such as ataxia, blurred vision, diplopia, and dizziness
 515 were dose related. Less common adverse reactions (<5%) were not assessed for dose-response
 516 relationships.

517 ***Monotherapy in Patients With Epilepsy:*** Adverse reactions observed in this study
 518 were generally similar to those observed and attributed to drug in adjunctive and monotherapy
 519 immediate-release lamotrigine and adjunctive LAMICTAL XR placebo-controlled studies. Only

520 2 adverse events, nasopharyngitis and upper respiratory tract infection, were observed at a rate of
521 $\geq 3\%$ and not reported at a similar rate in previous studies. Because this study did not include a
522 placebo control group, causality could not be established [see *Clinical Studies (14.3)*].

523 **6.2 Other Adverse Reactions Observed During the Clinical Development of** 524 **Immediate-Release Lamotrigine**

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

528 Adjunctive Therapy in Adults With Epilepsy: In addition to the adverse reactions
529 reported above from the development of LAMICTAL XR, the following adverse reactions with
530 an uncertain relationship to lamotrigine were reported during the clinical development of
531 immediate-release lamotrigine for treatment of epilepsy in adults. These reactions occurred in
532 $\geq 2\%$ of patients receiving immediate-release lamotrigine and more frequently than in the placebo
533 group.

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

535 *Musculoskeletal:* Arthralgia.

536 *Nervous:* Insomnia, convulsion, irritability, speech disorder, concentration
537 disturbance.

538 *Respiratory:* Pharyngitis, cough increased.

539 *Skin and Appendages:* Rash, pruritus.

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

541 Monotherapy in Adults With Epilepsy: In addition to the adverse reactions reported
542 above from the development of LAMICTAL XR, the following adverse reactions with an
543 uncertain relationship to lamotrigine were reported during the clinical development of
544 immediate-release lamotrigine for treatment of epilepsy in adults. These reactions occurred in
545 $> 2\%$ of patients receiving immediate-release lamotrigine and more frequently than in the placebo
546 group.

547 *Body as a Whole:* Chest pain.

548 *Digestive:* Rectal hemorrhage, peptic ulcer.

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

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

551 *Respiratory:* Epistaxis, dyspnea.

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

553 *Special Senses:* Vision abnormality.

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

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

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

560 defined as those occurring in at least 1/100 patients; *infrequent* adverse reactions are those
561 occurring in 1/100 to 1/1,000 patients; *rare* adverse reactions are those occurring in fewer than
562 1/1,000 patients.

563 *Cardiovascular System: Infrequent:* Hypertension, palpitations, postural
564 hypotension, syncope, tachycardia, vasodilation.

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

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

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

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

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

577 *Musculoskeletal System: Rare:* Muscle atrophy, pathological fracture, tendinous
578 contracture.

579 *Nervous System: Frequent:* Confusion. *Infrequent:* Akathisia, apathy, aphasia,
580 depersonalization, dysarthria, dyskinesia, euphoria, hallucinations, hostility, hyperkinesia,
581 hypertonia, libido decreased, memory decrease, mind racing, movement disorder, myoclonus,
582 panic attack, paranoid reaction, personality disorder, psychosis, stupor. *Rare:* Choreoathetosis,
583 delirium, delusions, dysphoria, dystonia, extrapyramidal syndrome, hemiplegia, hyperalgesia,
584 hyperesthesia, hypokinesia, hypotonia, manic depression reaction, neuralgia, paralysis,
585 peripheral neuritis.

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

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

591 *Urogenital System: Infrequent:* Abnormal ejaculation, hematuria, impotence,
592 menorrhagia, polyuria, urinary incontinence. *Rare:* Acute kidney failure, breast neoplasm,
593 creatinine increase, female lactation, kidney failure, kidney pain, nocturia, urinary retention,
594 urinary urgency.

595 **6.3 Postmarketing Experience With Immediate-Release Lamotrigine**

596 The following adverse events (not listed above in clinical trials or other sections of the
597 prescribing information) have been identified during postapproval use of immediate-release
598 lamotrigine. Because these events are reported voluntarily from a population of uncertain size, it

599 is not always possible to reliably estimate their frequency or establish a causal relationship to
 600 drug exposure.

601 Blood and Lymphatic: Agranulocytosis, hemolytic anemia, lymphadenopathy not
 602 associated with hypersensitivity disorder.

603 Gastrointestinal: Esophagitis.

604 Hepatobiliary Tract and Pancreas: Pancreatitis.

605 Immunologic: Lupus-like reaction, vasculitis.

606 Lower Respiratory: Apnea.

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

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

611 Non-site Specific: Progressive immunosuppression.

612 **7 DRUG INTERACTIONS**

613 Significant drug interactions with lamotrigine are summarized in Table 5. Additional
 614 details of these drug interaction studies, which were conducted using immediate-release
 615 lamotrigine, are provided in the Clinical Pharmacology section [*see Clinical Pharmacology*
 616 (*12.3*)].

617

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

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

Rifampin	↓ lamotrigine	Decreased lamotrigine AUC approximately 40%.
Valproate	↑ lamotrigine ? valproate	Increased lamotrigine concentrations slightly more than 2-fold. 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.

619 ↓ = Decreased (induces lamotrigine glucuronidation).

620 ↑ = Increased (inhibits lamotrigine glucuronidation).

621 ? = Conflicting data.

622 **8 USE IN SPECIFIC POPULATIONS**

623 **8.1 Pregnancy**

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

628 Pregnancy Category C.

629 There are no adequate and well-controlled studies in pregnant women. In animal studies,
 630 lamotrigine was developmentally toxic at doses lower than those administered clinically.
 631 LAMICTAL XR should be used during pregnancy only if the potential benefit justifies the
 632 potential risk to the fetus.

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

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

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

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

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

657 **8.2 Labor and Delivery**

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

659 **8.3 Nursing Mothers**

660 Preliminary data indicate that lamotrigine is excreted in human milk. Caution should be
661 exercised when LAMICTAL XR is administered to a nursing woman.

662 **8.4 Pediatric Use**

663 LAMICTAL XR is indicated as adjunctive therapy for PGTC and partial onset seizures
664 with or without secondary generalization in patients ≥ 13 years of age. Safety and effectiveness of
665 LAMICTAL XR for any use in patients less than 13 years of age have not been established.

666 Immediate-release lamotrigine is indicated for adjunctive therapy in patients ≥ 2 years of
667 age for partial seizures, the generalized seizures of Lennox-Gastaut syndrome, and PGTC
668 seizures.

669 Safety and efficacy of immediate-release lamotrigine, used as adjunctive treatment for
670 partial seizures, were not demonstrated in a small, randomized, double-blind, placebo-controlled
671 withdrawal study in very young pediatric patients (aged 1 to 24 months). Immediate-release
672 lamotrigine was associated with an increased risk for infectious adverse reactions (lamotrigine
673 37%, placebo 5%), and respiratory adverse reactions (lamotrigine 26%, placebo 5%). Infectious
674 adverse reactions included bronchiolitis, bronchitis, ear infection, eye infection, otitis externa,
675 pharyngitis, urinary tract infection, and viral infection. Respiratory adverse reactions included
676 nasal congestion, cough, and apnea.

677 In a juvenile animal study in which lamotrigine (oral doses of 5, 15, or 30 mg/kg) was
678 administered to young rats (postnatal days 7-62), decreased viability and growth were seen at the
679 highest dose tested and long-term behavioral abnormalities (decreased locomotor activity,
680 increased reactivity, and learning deficits in animals tested as adults) were observed at the two
681 highest doses. The no-effect dose for adverse effects on neurobehavioral development is less
682 than the human dose of 400 mg/day on a mg/m^2 basis.

683 **8.5 Geriatric Use**

684 Clinical studies of LAMICTAL XR for epilepsy did not include sufficient numbers of
685 subjects aged 65 years and over to determine whether they respond differently from younger
686 subjects or exhibit a different safety profile than that of younger patients. In general, dose
687 selection for an elderly patient should be cautious, usually starting at the low end of the dosing

688 range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of
689 concomitant disease or other drug therapy.

690 **8.6 Patients With Hepatic Impairment**

691 Experience in patients with hepatic impairment is limited. Based on a clinical
692 pharmacology study with immediate-release lamotrigine in 24 patients with mild, moderate, and
693 severe liver impairment [*see Clinical Pharmacology (12.3)*], the following general
694 recommendations can be made. No dosage adjustment is needed in patients with mild liver
695 impairment. Initial, escalation, and maintenance doses should generally be reduced by
696 approximately 25% in patients with moderate and severe liver impairment without ascites and
697 50% in patients with severe liver impairment with ascites. Escalation and maintenance doses
698 may be adjusted according to clinical response [*see Dosage and Administration (2.1)*].

699 **8.7 Patients With Renal Impairment**

700 Lamotrigine is metabolized mainly by glucuronic acid conjugation, with the majority of
701 the metabolites being recovered in the urine. In a small study comparing a single dose of
702 immediate-release lamotrigine in patients with varying degrees of renal impairment with healthy
703 volunteers, the plasma half-life of lamotrigine was approximately twice as long in the patients
704 with significant renal impairment [*see Clinical Pharmacology (12.3)*].

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

710 **10 OVERDOSAGE**

711 **10.1 Human Overdose Experience**

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

715 **10.2 Management of Overdose**

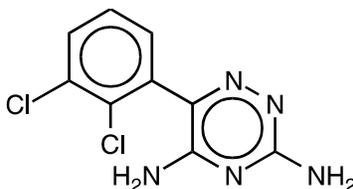
716 There are no specific antidotes for lamotrigine. Following a suspected overdose,
717 hospitalization of the patient is advised. General supportive care is indicated, including frequent
718 monitoring of vital signs and close observation of the patient. If indicated, emesis should be
719 induced;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

724 **11 DESCRIPTION**

725 LAMICTAL XR (lamotrigine), an AED of the phenyltriazine class, is chemically
726 unrelated to existing AEDs. Its chemical name is 3,5-diamino-6-(2,3-dichlorophenyl)-*as*-triazine,

727 its molecular formula is $C_9H_7N_5Cl_2$, and its molecular weight is 256.09. Lamotrigine is a white to
728 pale cream-colored powder and has a pK_a of 5.7. Lamotrigine is very slightly soluble in water
729 (0.17 mg/mL at 25°C) and slightly soluble in 0.1 M HCl (4.1 mg/mL at 25°C). The structural
730 formula is:

731



732

733

734 LAMICTAL XR Extended-Release Tablets are supplied for oral administration as 25-mg
735 (yellow with white center), 50-mg (green with white center), 100-mg (orange with white center),
736 200-mg (blue with white center), and 300-mg (gray with white center) tablets. Each tablet
737 contains the labeled amount of lamotrigine and the following inactive ingredients: glycerol
738 monostearate, hypromellose, lactose monohydrate, magnesium stearate, methacrylic acid
739 copolymer dispersion, polyethylene glycol 400, polysorbate 80, silicon dioxide (25-mg and 50-
740 mg tablets only), titanium dioxide, triethyl citrate, iron oxide black (50-mg and 300-mg tablets
741 only), iron oxide yellow (25-mg, 50-mg, 100-mg tablets only), iron oxide red (100-mg tablet
742 only), FD&C Blue No. 2 Aluminum Lake (200-mg tablet only). Tablets are printed with edible
743 black ink.

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

750 12 CLINICAL PHARMACOLOGY

751 12.1 Mechanism of Action

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

759 One proposed mechanism of action of lamotrigine, the relevance of which remains to be
760 established in humans, involves an effect on sodium channels. In vitro pharmacological studies
761 suggest that lamotrigine inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal

762 membranes and consequently modulating presynaptic transmitter release of excitatory amino
763 acids (e.g., glutamate and aspartate).

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

765 Lamotrigine did not inhibit N-methyl d-aspartate (NMDA)-induced depolarizations in rat cortical
766 slices or NMDA-induced cyclic GMP formation in immature rat cerebellum, nor did lamotrigine
767 displace compounds that are either competitive or noncompetitive ligands at this glutamate
768 receptor complex (CNQX, CGS, TCHP). The IC₅₀ for lamotrigine effects on NMDA-induced
769 currents (in the presence of 3 μM of glycine) in cultured hippocampal neurons exceeded
770 100 μM.

771 **12.2 Pharmacodynamics**

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

780 **Cardiovascular:** In dogs, lamotrigine is extensively metabolized to a 2-N-methyl
781 metabolite. This metabolite causes dose-dependent prolongation of the PR interval, widening of
782 the QRS complex, and, at higher doses, complete AV conduction block. Similar cardiovascular
783 effects are not anticipated in humans because only trace amounts of the 2-N-methyl metabolite
784 (<0.6% of lamotrigine dose) have been found in human urine [see *Clinical Pharmacology*
785 *(12.3)*]. However, it is conceivable that plasma concentrations of this metabolite could be
786 increased in patients with a reduced capacity to glucuronidate lamotrigine (e.g., in patients with
787 liver disease, patients taking concomitant medications that inhibit glucuronidation).

788 **12.3 Pharmacokinetics**

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

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

795 In an open-label, crossover study of 44 subjects with epilepsy receiving concomitant
796 AEDs, the steady-state pharmacokinetics of lamotrigine were compared following administration
797 of equivalent total doses of LAMICTAL XR given once daily with those of lamotrigine
798 immediate-release given twice daily. In this study, the median time to peak concentration (T_{max})
799 following administration of LAMICTAL XR was 4 to 6 hours in patients taking carbamazepine,
800 phenytoin, phenobarbital, or primidone; 9 to 11 hours in patients taking valproate; and 6 to 10
801 hours in patients taking AEDs other than carbamazepine, phenytoin, phenobarbital, primidone,

802 or valproate. In comparison, the median T_{max} following administration of immediate-release
803 lamotrigine was between 1 and 1.5 hours.

804 The steady-state trough concentrations for extended-release lamotrigine were similar to
805 or higher than those of immediate-release lamotrigine depending on concomitant AED (Table 6).
806 A mean reduction in the lamotrigine C_{max} by 11% to 29% was observed for LAMICTAL XR
807 compared to immediate-release lamotrigine, resulting in a decrease in the peak-to-trough
808 fluctuation in serum lamotrigine concentrations. However, in some subjects receiving enzyme-
809 inducing AEDs, a reduction in C_{max} of 44% to 77% was observed. The degree of fluctuation was
810 reduced by 17% in patients taking enzyme-inducing AEDs; 34% in patients taking valproate; and
811 37% in patients taking AEDs other than carbamazepine, phenytoin, phenobarbital, primidone, or
812 valproate. LAMICTAL XR and immediate-release lamotrigine regimens were similar with
813 respect to area under the curve (AUC, a measure of the extent of bioavailability) for patients
814 receiving AEDs other than those known to induce the metabolism of lamotrigine. The relative
815 bioavailability of extended-release lamotrigine was approximately 21% lower than immediate-
816 release lamotrigine in subjects receiving enzyme-inducing AEDs. However, a reduction in
817 exposure of up to 70% was observed in some subjects in this group when they switched to
818 LAMICTAL XR. Therefore, doses may need to be adjusted in some subjects based on
819 therapeutic response.

820

821 **Table 6. Steady-State Bioavailability of LAMICTAL XR Relative to Immediate-Release**
822 **Lamotrigine at Equivalent Daily Doses (Ratio of Extended-Release to Immediate-Release**
823 **90% CI)**

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

824 ^a Enzyme-inducing antiepileptic drugs include carbamazepine, phenytoin, phenobarbital, and
825 primidone.

826

827 **Dose Proportionality:** In healthy volunteers not receiving any other medications and
828 given LAMICTAL XR once daily, the systemic exposure to lamotrigine increased in direct
829 proportion to the dose administered over the range of 50 to 200 mg. At doses between 25 and
830 50 mg, the increase was less than dose proportional, with a 2-fold increase in dose resulting in an
831 approximately 1.6-fold increase in systemic exposure.

832 **Distribution:** Estimates of the mean apparent volume of distribution (Vd/F) of
833 lamotrigine following oral administration ranged from 0.9 to 1.3 L/kg. Vd/F is independent of

834 dose and is similar following single and multiple doses in both patients with epilepsy and in
835 healthy volunteers.

836 **Protein Binding:** Data from in vitro studies indicate that lamotrigine is approximately
837 55% bound to human plasma proteins at plasma lamotrigine concentrations from 1 to 10 mcg/mL
838 (10 mcg/mL is 4 to 6 times the trough plasma concentration observed in the controlled efficacy
839 trials). Because lamotrigine is not highly bound to plasma proteins, clinically significant
840 interactions with other drugs through competition for protein binding sites are unlikely. The
841 binding of lamotrigine to plasma proteins did not change in the presence of therapeutic
842 concentrations of phenytoin, phenobarbital, or valproate. Lamotrigine did not displace other
843 AEDs (carbamazepine, phenytoin, phenobarbital) from protein-binding sites.

844 **Metabolism:** Lamotrigine is metabolized predominantly by glucuronic acid conjugation;
845 the major metabolite is an inactive 2-N-glucuronide conjugate. After oral administration of
846 240 mg of ¹⁴C-lamotrigine (15 μCi) to 6 healthy volunteers, 94% was recovered in the urine and
847 2% was recovered in the feces. The radioactivity in the urine consisted of unchanged lamotrigine
848 (10%), the 2-N-glucuronide (76%), a 5-N-glucuronide (10%), a 2-N-methyl metabolite (0.14%),
849 and other unidentified minor metabolites (4%).

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

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

859 **Elimination:** The elimination half-life and apparent clearance of lamotrigine following
860 oral administration of immediate-release lamotrigine to adult patients with epilepsy and healthy
861 volunteers is summarized in Table 7. Half-life and apparent clearance vary depending on
862 concomitant AEDs.

863 Since the half-life of lamotrigine following administration of single doses of immediate-
864 release lamotrigine is comparable to that observed following administration of LAMICTAL XR,
865 similar changes in the half-life of lamotrigine would be expected for LAMICTAL XR.

866

867 **Table 7. Mean^a Pharmacokinetic Parameters of Immediate-Release Lamotrigine in**
 868 **Healthy Volunteers and Adult Patients With Epilepsy**

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

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

874 ^b Carbamazepine, phenobarbital, phenytoin, and primidone have been shown to increase the
 875 apparent clearance of lamotrigine. Estrogen-containing oral contraceptives and other drugs
 876 such as rifampin that induce lamotrigine glucuronidation have also been shown to increase
 877 the apparent clearance of lamotrigine [see *Drug Interactions (7)*].
 878

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

882 The net effects of drug interactions with lamotrigine are summarized in Table 8. Details
 883 of the drug interaction studies, which were done using immediate-release lamotrigine, are
 884 provided in Table 8.
 885

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

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

887 ^a From adjunctive clinical trials and volunteer studies.

- 888 ^b Net effects were estimated by comparing the mean clearance values obtained in adjunctive
889 clinical trials and volunteer studies.
- 890 ^c The effect of other hormonal contraceptive preparations or hormone replacement therapy on
891 the pharmacokinetics of lamotrigine has not been systematically evaluated in clinical trials,
892 although the effect may be similar to that seen with the ethinylestradiol/levonorgestrel
893 combinations.
- 894 ^d Modest decrease in levonorgestrel.
- 895 ^e Not administered, but an active metabolite of carbamazepine.
- 896 ^f Slight decrease, not expected to be clinically relevant.
- 897 ^g Not administered, but an active metabolite of oxcarbazepine.
- 898 ^h Slight increase, not expected to be clinically relevant.
- 899 ↔ = No significant effect.
- 900 ? = Conflicting data.
- 901

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

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

916 In the same study, coadministration of lamotrigine (300 mg/day) in 16 female volunteers
917 did not affect the pharmacokinetics of the ethinylestradiol component of the oral contraceptive
918 preparation. There were mean decreases in the AUC and C_{max} of the levonorgestrel component of
919 19% and 12%, respectively. Measurement of serum progesterone indicated that there was no
920 hormonal evidence of ovulation in any of the 16 volunteers, although measurement of serum
921 FSH, LH, and estradiol indicated that there was some loss of suppression of the hypothalamic-
922 pituitary-ovarian axis.

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

925 The clinical significance of the observed hormonal changes on ovulatory activity is
926 unknown. However, the possibility of decreased contraceptive efficacy in some patients cannot

927 be excluded. Therefore, patients should be instructed to promptly report changes in their
928 menstrual pattern (e.g., break-through bleeding).

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

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

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

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

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

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

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

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

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

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

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

967 Olanzapine: The AUC and C_{\max} of olanzapine were similar following the addition of
968 olanzapine (15 mg once daily) to lamotrigine (200 mg once daily) in healthy male volunteers (n
969 = 16) compared with the AUC and C_{\max} in healthy male volunteers receiving olanzapine alone (n
970 = 16).

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

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

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

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

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

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

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

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

998 Valproate: When lamotrigine was administered to healthy volunteers (n = 18) receiving
999 valproate, the trough steady-state valproate plasma concentrations decreased by an average of
1000 25% over a 3-week period, and then stabilized. However, adding lamotrigine to the existing
1001 therapy did not cause a change in valproate plasma concentrations in either adult or pediatric
1002 patients in controlled clinical trials.

1003 The addition of valproate increased lamotrigine steady-state concentrations in normal
1004 volunteers by slightly more than 2-fold. In one study, maximal inhibition of lamotrigine
1005 clearance was reached at valproate doses between 250 and 500 mg/day and did not increase as
1006 the valproate dose was further increased.

1007 **Zonisamide:** In a study of 18 patients with epilepsy, coadministration of zonisamide
1008 (200 to 400 mg/day) with lamotrigine (150 to 500 mg/day for 35 days) had no significant effect
1009 on the pharmacokinetics of lamotrigine.

1010 **Known Inducers or Inhibitors of Glucuronidation:** Drugs other than those listed above
1011 have not been systematically evaluated in combination with lamotrigine. Since lamotrigine is
1012 metabolized predominately by glucuronic acid conjugation, drugs that are known to induce or
1013 inhibit glucuronidation may affect the apparent clearance of lamotrigine, and doses of
1014 LAMICTAL XR may require adjustment based on clinical response.

1015 **Other:** Results of in vitro experiments suggest that clearance of lamotrigine is unlikely to
1016 be reduced by concomitant administration of amitriptyline, clonazepam, clozapine, fluoxetine,
1017 haloperidol, lorazepam, phenelzine, risperidone, sertraline, or trazodone.

1018 Results of in vitro experiments suggest that lamotrigine does not reduce the clearance of
1019 drugs eliminated predominantly by CYP2D6.

1020 **Special Populations: Patients With Renal Impairment:** Twelve volunteers with
1021 chronic renal failure (mean creatinine clearance: 13 mL/min, range: 6 to 23) and another 6
1022 individuals undergoing hemodialysis were each given a single 100-mg dose of immediate-release
1023 lamotrigine. The mean plasma half-lives determined in the study were 42.9 hours (chronic renal
1024 failure), 13.0 hours (during hemodialysis), and 57.4 hours (between hemodialysis) compared
1025 with 26.2 hours in healthy volunteers. On average, approximately 20% (range: 5.6 to 35.1) of the
1026 amount of lamotrigine present in the body was eliminated by hemodialysis during a 4-hour
1027 session [*see Dosage and Administration (2.1)*].

1028 **Hepatic Disease:** The pharmacokinetics of lamotrigine following a single 100-mg
1029 dose of immediate-release lamotrigine were evaluated in 24 subjects with mild, moderate, and
1030 severe hepatic impairment (Child-Pugh Classification system) and compared with 12 subjects
1031 without hepatic impairment. The patients with severe hepatic impairment were without ascites
1032 (n = 2) or with ascites (n = 5). The mean apparent clearances of lamotrigine in patients with mild
1033 (n = 12), moderate (n = 5), severe without ascites (n = 2), and severe with ascites (n = 5) liver
1034 impairment were 0.30 ± 0.09 , 0.24 ± 0.1 , 0.21 ± 0.04 , and 0.15 ± 0.09 mL/min/kg, respectively,
1035 as compared with 0.37 ± 0.1 mL/min/kg in the healthy controls. Mean half-lives of lamotrigine
1036 in patients with mild, moderate, severe without ascites, and severe with ascites hepatic
1037 impairment were 46 ± 20 , 72 ± 44 , 67 ± 11 , and 100 ± 48 hours, respectively, as compared with
1038 33 ± 7 hours in healthy controls [*see Dosage and Administration (2.1)*].

1039 **Elderly:** The pharmacokinetics of lamotrigine following a single 150-mg dose of
1040 immediate-release lamotrigine were evaluated in 12 elderly volunteers between the ages of 65
1041 and 76 years (mean creatinine clearance: 61 mL/min, range: 33 to 108 mL/min). The mean half-
1042 life of lamotrigine in these subjects was 31.2 hours (range: 24.5 to 43.4 hours), and the mean
1043 clearance was 0.40 mL/min/kg (range: 0.26 to 0.48 mL/min/kg).

1044 **Gender:** The clearance of lamotrigine is not affected by gender. However, during
1045 dose escalation of immediate-release lamotrigine in one clinical trial in patients with epilepsy on

1046 a stable dose of valproate (n = 77), mean trough lamotrigine concentrations, unadjusted for
1047 weight, were 24% to 45% higher (0.3 to 1.7 mcg/mL) in females than in males.

1048 *Race:* The apparent oral clearance of lamotrigine was 25% lower in non-Caucasians
1049 than Caucasians.

1050 *Pediatric Patients:* Safety and effectiveness of LAMICTAL XR for use in patients
1051 less than 13 years of age have not been established.

1052 **13 NONCLINICAL TOXICOLOGY**

1053 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

1054 No evidence of carcinogenicity was seen in mouse or rat following oral administration of
1055 lamotrigine for up to 2 years at doses up to 30 mg/kg/day and 10 to 15 mg/kg/day in mouse and
1056 rat, respectively. The highest doses tested are less than the human dose of 400 mg/day on a body
1057 surface area (mg/m²) basis.

1058 Lamotrigine was negative in *in vitro* gene mutation (Ames and mouse lymphoma *tk*)
1059 assays and in clastogenicity (*in vitro* human lymphocyte and *in vivo* rat bone marrow) assays.

1060 No evidence of impaired fertility was detected in rats given oral doses of lamotrigine up
1061 to 20 mg/kg/day. The highest dose tested is less than the human dose of 400 mg/day on a mg/m²
1062 basis.

1063 **14 CLINICAL STUDIES**

1064 **14.1 Adjunctive Therapy for Primary Generalized Tonic-Clonic Seizures**

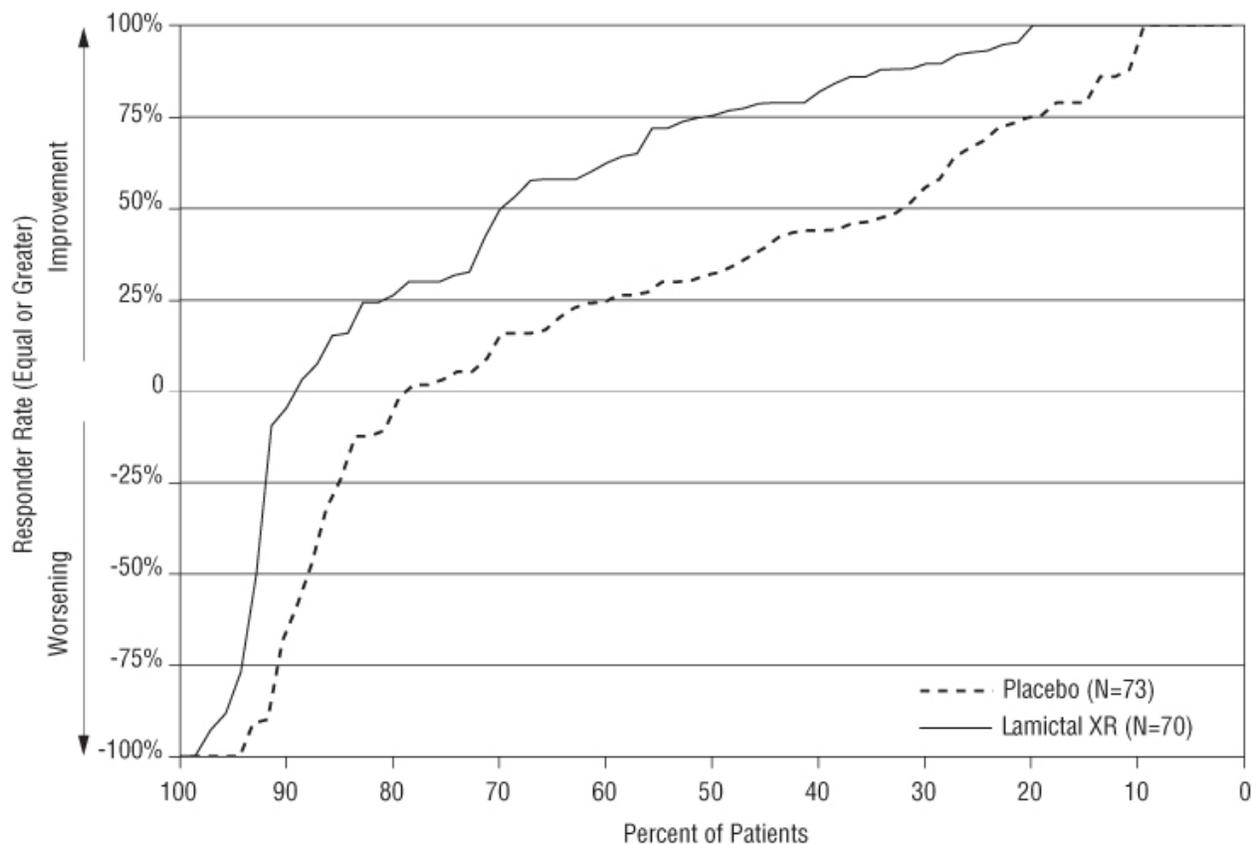
1065 The effectiveness of LAMICTAL XR as adjunctive therapy was established in PGTC
1066 seizures in a 19-week, international, multicenter, double-blind, randomized, placebo-controlled
1067 study in 143 patients 13 years of age and older (n = 70 on LAMICTAL XR and n = 73 on
1068 placebo). Patients with at least 3 PGTC seizures during an 8-week baseline phase were
1069 randomized to 19 weeks of treatment with LAMICTAL XR or placebo added to their current
1070 AED regimen of up to 2 drugs. Patients were dosed on a fixed-dose regimen, with target doses
1071 ranging from 200 to 500 mg/day of LAMICTAL XR based on concomitant AED(s) (target dose
1072 = 200 mg for valproate, 300 mg for AEDs not altering plasma lamotrigine levels, and 500 mg for
1073 enzyme-inducing AEDs).

1074 The primary efficacy endpoint was percent change from baseline in PGTC seizure
1075 frequency during the double-blind treatment phase. For the intent-to-treat population, the median
1076 percent reduction in PGTC seizure frequency was 75% in patients treated with LAMICTAL XR
1077 and 32% in patients treated with placebo, a difference that was statistically significant, defined as
1078 a 2-sided *P* value ≤ 0.05 .

1079 Figure 1 presents the percentage of patients (X-axis) with a percent reduction in PGTC
1080 seizure frequency (responder rate) from baseline through the entire treatment period at least as
1081 great as that represented on the Y-axis. A positive value on the Y-axis indicates an improvement
1082 from baseline (i.e., a decrease in seizure frequency), while a negative value indicates a worsening
1083 from baseline (i.e., an increase in seizure frequency). Thus, in a display of this type, a curve for
1084 an effective treatment is shifted to the left of the curve for placebo. The proportion of patients

1085 achieving any particular level of reduction in PGTC seizure frequency was consistently higher
1086 for the group treated with LAMICTAL XR compared with the placebo group. For example, 70%
1087 of patients randomized to LAMICTAL XR experienced a 50% or greater reduction in PGTC
1088 seizure frequency, compared with 32% of patients randomized to placebo. Patients with an
1089 increase in seizure frequency >100% are represented on the Y-axis as equal to or greater than
1090 -100%.

1091
1092 **Figure 1. Proportion of Patients by Responder Rate for LAMICTAL XR and Placebo**
1093 **Group (Primary Generalized Tonic-Clonic Seizures Study)**



1094
1095 **14.2 Adjunctive Therapy for Partial Onset Seizures**
1096 The effectiveness of immediate-release lamotrigine as adjunctive therapy was initially
1097 established in 3 pivotal, multicenter, placebo-controlled, double-blind clinical trials in 355 adults
1098 with refractory partial onset seizures.

1099 The effectiveness of LAMICTAL XR as adjunctive therapy in partial onset seizures, with
1100 or without secondary generalization, was established in a 19-week, multicenter, double-blind,
1101 placebo-controlled trial in 236 patients 13 years of age and older (approximately 93% of patients
1102 were aged 16 to 65 years). Approximately 36% were from the U.S. and approximately 64% were
1103 from other countries including Argentina, Brazil, Chile, Germany, India, Korea, Russian
1104 Federation, and Ukraine. Patients with at least 8 partial onset seizures during an 8-week
1105 prospective baseline phase (or 4-week prospective baseline coupled with a 4-week historical

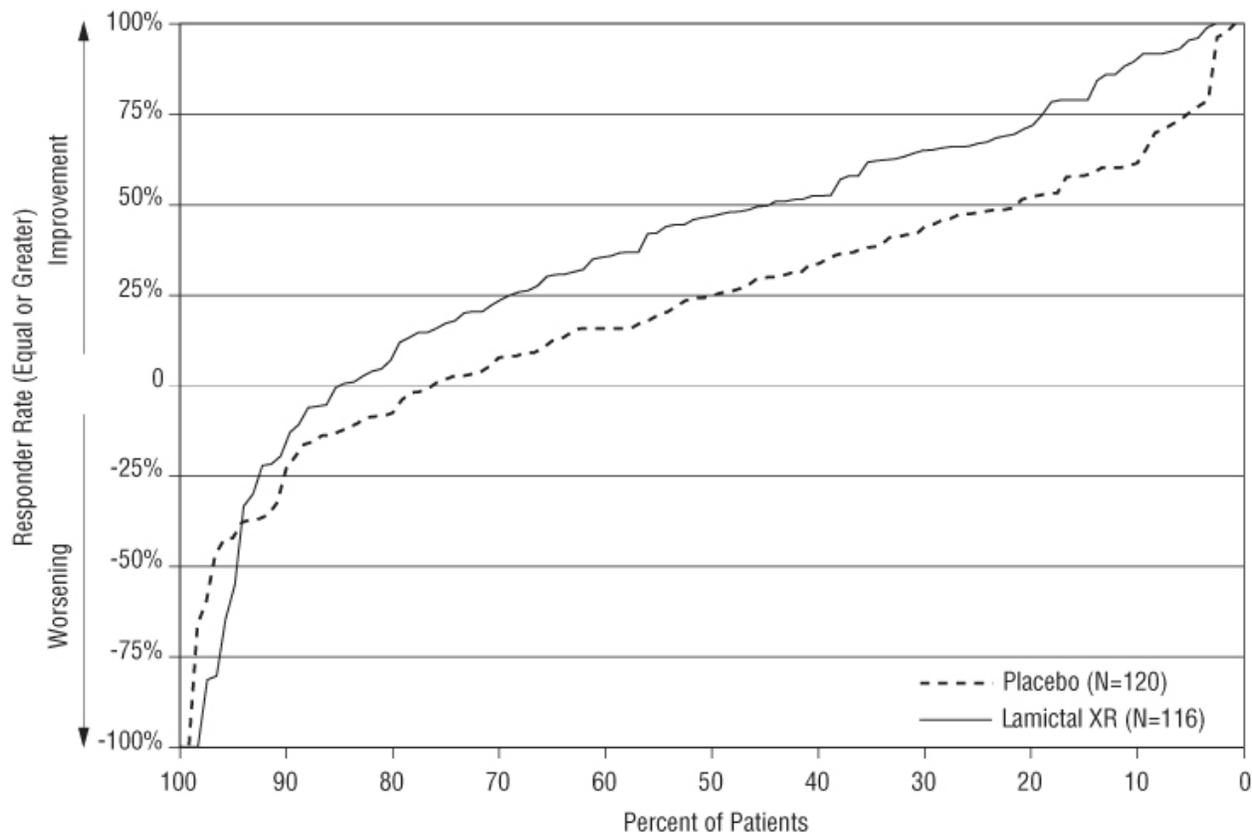
1106 baseline documented with seizure diary data) were randomized to treatment with
1107 LAMICTAL XR (n = 116) or placebo (n = 120) added to their current regimen of 1 or 2 AEDs.
1108 Approximately half of the patients were taking 2 concomitant AEDs at baseline. Target doses
1109 ranged from 200 to 500 mg/day of LAMICTAL XR based on concomitant AED (target dose =
1110 200 mg for valproate, 300 mg for AEDs not altering plasma lamotrigine, and 500 mg for
1111 enzyme-inducing AEDs). The median partial seizure frequency per week at baseline was 2.3 for
1112 LAMICTAL XR and 2.1 for placebo.

1113 The primary endpoint was the median percent change from baseline in partial onset
1114 seizure frequency during the entire double-blind treatment phase. The median percent reductions
1115 in weekly partial onset seizures were 47% in patients treated with LAMICTAL XR and 25% on
1116 placebo, a difference that was statistically significant, defined as a 2-sided *P* value ≤ 0.05 .

1117 Figure 2 presents the percentage of patients (X-axis) with a percent reduction in partial
1118 seizure frequency (responder rate) from baseline through the entire treatment period at least as
1119 great as that represented on the Y-axis. The proportion of patients achieving any particular level
1120 of reduction in partial seizure frequency was consistently higher for the group treated with
1121 LAMICTAL XR compared with the placebo group. For example, 44% of patients randomized to
1122 LAMICTAL XR experienced a 50% or greater reduction in partial seizure frequency compared
1123 with 21% of patients randomized to placebo.

1124

1125 **Figure 2. Proportion of Patients by Responder Rate for LAMICTAL XR and Placebo**
1126 **Group (Partial Onset Seizure Study)**



1127
1128

1129 **14.3 Conversion to Monotherapy for Partial Onset Seizures**

1130 The effectiveness of LAMICTAL XR as monotherapy for partial onset seizures was
1131 established in a historical-control trial in 223 adults with partial seizures. The historical control
1132 methodology is described in a publication by French, et al. [see References (15)]. Briefly, in this
1133 study, patients were randomized to ultimately receive either Lamictal XR 300 mg or 250 mg
1134 once a day, and their responses were compared to those of a historical control group. The
1135 historical control consisted of a pooled analysis of the control groups from 8 studies of similar
1136 design, which utilized a subtherapeutic dose of an AED as a comparator. Statistical superiority to
1137 the historical control was considered to be demonstrated if the upper 95% confidence interval for
1138 the proportion of patients meeting escape criteria in patients receiving LAMICTAL XR remained
1139 below the lower 95% prediction interval of 65.3% derived from the historical control data.

1140 In this study, patients ≥ 13 years of age experienced at least 4 partial seizures during an 8-
1141 week baseline period with at least 2 seizures occurring during each of 2 consecutive 4-week
1142 periods while receiving valproate or a non-enzyme-inducing AED. LAMICTAL XR was added
1143 to either valproate or a non-enzyme-inducing AED over a 6- to 7-week period followed by the
1144 gradual withdrawal of the background AED. Patients were then continued on monotherapy with
1145 LAMICTAL XR for 12 weeks. The escape criteria were one or more of the following:

1146 (1) doubling of average monthly seizure count during any 28 consecutive days, (2) doubling of
1147 highest consecutive 2-day seizure frequency during the entire treatment phase, (3) emergence of
1148 a new seizure type compared to baseline (4) clinically significant prolongation of generalized
1149 tonic-clonic seizures or worsening of seizure considered by the investigator to require
1150 intervention. These criteria were similar to those in the 8 controlled trials from which the
1151 historical control group was constituted.

1152 The upper 95% confidence limits of the proportion of subjects meeting escape criteria
1153 (40.2% at 300 mg/day and 44.5% at 250 mg/day) were below the threshold of 65.3% derived
1154 from the historical control data.

1155 Although the study population was not fully comparable to the historical controlled
1156 population and the study was not fully blinded, numerous sensitivity analyses supported the
1157 primary results. Efficacy was further supported by the established effectiveness of the
1158 immediate-release formulation as monotherapy.

1159 **15 REFERENCES**

1160 1. French JA, Wang S, Warnock B, Temkin N. Historical control monotherapy design in the
1161 treatment of epilepsy. *Epilepsia*. 2010; 54:1936-1943.

1162 **16 HOW SUPPLIED/STORAGE AND HANDLING**

1163 **LAMICTAL XR (lamotrigine) Extended-Release Tablets**

1164 25 mg, yellow with a white center, round, biconvex, film-coated tablets printed on one
1165 face in black ink with "LAMICTAL" and "XR 25", unit-of-use bottles of 30 with orange caps
1166 (NDC 0173-0754-00).

1167 50 mg, green with a white center, round, biconvex, film-coated tablets printed on one
1168 face in black ink with "LAMICTAL" and "XR 50", unit-of-use bottles of 30 with orange caps
1169 (NDC 0173-0755-00).

1170 100 mg, orange with a white center, round, biconvex, film-coated tablets printed on one
1171 face in black ink with "LAMICTAL" and "XR 100", unit-of-use bottles of 30 with orange caps
1172 (NDC 0173-0756-00).

1173 200 mg, blue with a white center, round, biconvex, film-coated tablets printed on one
1174 face in black ink with "LAMICTAL" and "XR 200", unit-of-use bottles of 30 with orange caps
1175 (NDC 0173-0757-00).

1176 300 mg, gray with a white center, caplet-shaped, film-coated tablets printed on one face
1177 in black ink with "LAMICTAL" and "XR 300", unit-of-use bottles of 30 with orange caps (NDC
1178 0173-0761-00).

1179 **LAMICTAL XR (lamotrigine) Patient Titration Kit for Patients Taking Valproate** 1180 **(Blue XR Kit)**

1181 25 mg, yellow with a white center, round, biconvex, film-coated tablets printed on one
1182 face in black ink with "LAMICTAL" and "XR 25" and 50 mg, green with a white center, round,
1183 biconvex, film-coated tablets printed on one face in black ink with "LAMICTAL" and "XR 50";
1184 blisterpack of 21/25-mg tablets and 7/50-mg tablets (NDC 0173-0758-00).

1185 **LAMICTAL XR (lamotrigine) Patient Titration Kit for Patients Taking**
1186 **Carbamazepine, Phenytoin, Phenobarbital, or Primidone, and Not Taking Valproate**
1187 **(Green XR Kit)**

1188 50 mg, green with a white center, round, biconvex, film-coated tablets printed on one
1189 face in black ink with “LAMICTAL” and “XR 50”; 100 mg, orange with a white center, round,
1190 biconvex, film-coated tablets printed on one face in black ink with “LAMICTAL” and “XR
1191 100”; and 200 mg, blue with a white center, round, biconvex, film-coated tablets printed on one
1192 face in black ink with “LAMICTAL” and “XR 200”; blisterpack of 14/50-mg tablets, 14/100-mg
1193 tablets, and 7/200-mg tablets (NDC 0173-0759-00).

1194 **LAMICTAL XR (lamotrigine) Patient Titration Kit for Patients Not Taking**
1195 **Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate (Orange XR Kit)**

1196 25 mg, yellow with a white center, round, biconvex, film-coated tablets printed on one
1197 face in black ink with “LAMICTAL” and “XR 25”; 50 mg, green with a white center, round,
1198 biconvex, film-coated tablets printed on one face in black ink with “LAMICTAL” and “XR 50”;
1199 and 100 mg, orange with a white center, round, biconvex, film-coated tablets printed on one face
1200 in black ink with “LAMICTAL” and “XR 100”; blisterpack of 14/25-mg tablets, 14/50-mg
1201 tablets, and 7/100-mg tablets (NDC 0173-0760-00).

1202 **Storage:** Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP
1203 Controlled Room Temperature].

1204 **17 PATIENT COUNSELING INFORMATION**

1205 *See FDA-approved patient labeling (Medication Guide).*

1206 **17.1 Rash**

1207 Prior to initiation of treatment with LAMICTAL XR, the patient should be instructed that
1208 a rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy) may herald
1209 a serious medical event and that the patient should report any such occurrence to a physician
1210 immediately.

1211 **17.2 Suicidal Thinking and Behavior**

1212 Patients, their caregivers, and families should be counseled that AEDs, including
1213 LAMICTAL XR, may increase the risk of suicidal thoughts and behavior and should be advised
1214 of the need to be alert for the emergence or worsening of symptoms of depression; any unusual
1215 changes in mood or behavior; or the emergence of suicidal thoughts, behavior, or thoughts about
1216 self-harm. Behaviors of concern should be reported immediately to healthcare providers.

1217 **17.3 Worsening of Seizures**

1218 Patients should be advised to notify their physicians if worsening of seizure control
1219 occurs.

1220 **17.4 Central Nervous System Adverse Effects**

1221 Patients should be advised that LAMICTAL XR may cause dizziness, somnolence, and
1222 other symptoms and signs of central nervous system depression. Accordingly, they should be
1223 advised neither to drive a car nor to operate other complex machinery until they have gained

1224 sufficient experience on LAMICTAL XR to gauge whether or not it adversely affects their
1225 mental and/or motor performance.

1226 **17.5 Blood Dyscrasias and/or Acute Multiorgan Failure**

1227 Patients should be advised of the possibility of blood dyscrasias and/or acute multiorgan
1228 failure and to contact their physician immediately if they experience any signs or symptoms of
1229 these conditions [*see Warnings and Precautions (5.3, 5.4)*].

1230 **17.6 Pregnancy**

1231 Patients should be advised to notify their physicians if they become pregnant or intend to
1232 become pregnant during therapy. Patients should be advised to notify their physicians if they
1233 intend to breastfeed or are breastfeeding an infant.

1234 Patients should also be encouraged to enroll in the NAAED Pregnancy Registry if they
1235 become pregnant. This registry is collecting information about the safety of antiepileptic drugs
1236 during pregnancy. To enroll, patients can call the toll-free number 1-888-233-2334 [*see Use in*
1237 *Specific Populations (8.1)*].

1238 **17.7 Oral Contraceptive Use**

1239 Women should be advised to notify their physicians if they plan to start or stop use of
1240 oral contraceptives or other female hormonal preparations. Starting estrogen-containing oral
1241 contraceptives may significantly decrease lamotrigine plasma levels and stopping estrogen-
1242 containing oral contraceptives (including the pill-free week) may significantly increase
1243 lamotrigine plasma levels [*see Warnings and Precautions (5.8), Clinical Pharmacology (12.3)*].
1244 Women should also be advised to promptly notify their physicians if they experience adverse
1245 reactions or changes in menstrual pattern (e.g., break-through bleeding) while receiving
1246 LAMICTAL XR in combination with these medications.

1247 **17.8 Discontinuing LAMICTAL XR**

1248 Patients should be advised to notify their physicians if they stop taking LAMICTAL XR
1249 for any reason and not to resume LAMICTAL XR without consulting their physicians.

1250 **17.9 Aseptic Meningitis**

1251 Patients should be advised that LAMICTAL XR may cause aseptic meningitis. Patients
1252 should be advised to notify their physicians immediately if they develop signs and symptoms of
1253 meningitis such as headache, fever, nausea, vomiting, stiff neck, rash, abnormal sensitivity to
1254 light, myalgia, chills, confusion, or drowsiness while taking LAMICTAL XR.

1255 **17.10 Potential Medication Errors**

1256 Medication errors involving LAMICTAL have occurred. In particular the names
1257 LAMICTAL or lamotrigine can be confused with the names of other commonly used
1258 medications. Medication errors may also occur between the different formulations of
1259 LAMICTAL. To reduce the potential of medication errors, write and say LAMICTAL XR
1260 clearly. Depictions of the LAMICTAL XR Extended-Release Tablets can be found in the
1261 Medication Guide. Each LAMICTAL XR tablet has a distinct color and white center, and is
1262 printed with "LAMICTAL XR" and the tablet strength. These distinctive features serve to
1263 identify the different presentations of the drug and thus may help reduce the risk of medication

1264 errors. LAMICTAL XR is supplied in round, unit-of-use bottles with orange caps containing 30
1265 tablets. The label on the bottle includes a depiction of the tablets that further communicates to
1266 patients and pharmacists that the medication is LAMICTAL XR and the specific tablet strength
1267 included in the bottle. The unit-of-use bottle with a distinctive orange cap and distinctive bottle
1268 label features serves to identify the different presentations of the drug and thus may help to
1269 reduce the risk of medication errors. **To avoid a medication error of using the wrong drug or**
1270 **formulation, patients should be strongly advised to visually inspect their tablets to verify**
1271 **that they are LAMICTAL XR each time they fill their prescription and to immediately talk**
1272 **to their doctor/pharmacist if they receive a LAMICTAL XR tablet without a white center**
1273 **and without “LAMICTAL XR” and the strength printed on the tablet as they may have**
1274 **received the wrong medication** [see *Dosage Forms and Strengths (3), How Supplied/Storage*
1275 *and Handling (16)*].

1276
1277 LAMICTAL XR and DiffCORE are trademarks of GlaxoSmithKline.

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1282 Research Triangle Park, NC 27709

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1290 MEDICATION GUIDE

1291

1292 LAMICTAL[®] (la-MIK-tal) XR[™] (lamotrigine) Extended-Release Tablets

1293

1294 Read this Medication Guide before you start taking LAMICTAL XR and each time you get a
1295 refill. There may be new information. This information does not take the place of talking with
1296 your healthcare provider about your medical condition or treatment. If you have questions about
1297 LAMICTAL XR, ask your healthcare provider or pharmacist.

1298

1299 **What is the most important information I should know about LAMICTAL XR?**

1300 **1. LAMICTAL XR may cause a serious skin rash that may cause you to be hospitalized or**
1301 **to stop LAMICTAL XR; it may rarely cause death.**

1302 There is no way to tell if a mild rash will develop into a more serious reaction. These serious
1303 skin reactions are more likely to happen when you begin taking LAMICTAL XR, within the
1304 first 2 to 8 weeks of treatment. But it can happen in people who have taken LAMICTAL XR
1305 for any period of time. Children between 2 to 16 years of age have a higher chance of getting
1306 this serious skin reaction while taking lamotrigine. LAMICTAL XR is not approved for use
1307 in children less than 13 years of age.

1308 The risk of getting a rash is higher if you:

- 1309 • take LAMICTAL XR while taking valproate [DEPAKENE (valproic acid) or
1310 DEPAKOTE (divalproex sodium)].
- 1311 • take a higher starting dose of LAMICTAL XR than your healthcare provider prescribed.
- 1312 • increase your dose of LAMICTAL XR faster than prescribed.

1313 **LAMICTAL XR can also cause other types of allergic reactions or serious problems**
1314 **that may affect organs and other parts of your body like the liver or blood cells. You**
1315 **may or may not have a rash with these types of reactions.**

1316 **Call your healthcare provider right away if you have any of the following:**

- 1317 • **a skin rash**
- 1318 • **hives**
- 1319 • **fever**
- 1320 • **swollen lymph glands**
- 1321 • **painful sores in the mouth or around your eyes**
- 1322 • **swelling of your lips or tongue**
- 1323 • **yellowing of your skin or eyes**
- 1324 • **unusual bruising or bleeding**
- 1325 • **severe fatigue or weakness**
- 1326 • **severe muscle pain**
- 1327 • **frequent infections**

1328 These symptoms may be the first signs of a serious reaction. A healthcare provider should
1329 examine you to decide if you should continue taking LAMICTAL XR.

1330 **2. Like other antiepileptic drugs, LAMICTAL XR may cause suicidal thoughts or actions**
1331 **in a very small number of people, about 1 in 500.**

1332 **Call a healthcare provider right away if you have any of these symptoms, especially if**
1333 **they are new, worse, or worry you:**

- 1334 • thoughts about suicide or dying
- 1335 • attempt to commit suicide
- 1336 • new or worse depression
- 1337 • new or worse anxiety
- 1338 • feeling agitated or restless
- 1339 • panic attacks

- 1340 • trouble sleeping (insomnia)
- 1341 • new or worse irritability
- 1342 • acting aggressive, being angry, or violent
- 1343 • acting on dangerous impulses
- 1344 • an extreme increase in activity and talking (mania)
- 1345 • other unusual changes in behavior or mood

1346 **Do not stop LAMICTAL XR without first talking to a healthcare provider.**

- 1347 • Stopping LAMICTAL XR suddenly can cause serious problems.
- 1348 • Suicidal thoughts or actions can be caused by things other than medicines. If you have
- 1349 suicidal thoughts or actions, your healthcare provider may check for other causes.

1350 **How can I watch for early symptoms of suicidal thoughts and actions?**

- 1351 • Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or
- 1352 feelings.
- 1353 • Keep all follow-up visits with your healthcare provider as scheduled.
- 1354 • Call your healthcare provider between visits as needed, especially if you are worried
- 1355 about symptoms.

1356 **3. LAMICTAL XR may rarely cause aseptic meningitis, a serious inflammation of the**
1357 **protective membrane that covers the brain and spinal cord.**

1358 **Call your healthcare provider right away if you have any of the following symptoms:**

- 1359 • Headache
- 1360 • Fever
- 1361 • Nausea
- 1362 • Vomiting
- 1363 • Stiff neck
- 1364 • Rash
- 1365 • Unusual sensitivity to light
- 1366 • Muscle pains
- 1367 • Chills
- 1368 • Confusion
- 1369 • Drowsiness

1370 Meningitis has many causes other than LAMICTAL XR, which your doctor would check for
1371 if you developed meningitis while taking LAMICTAL XR.

1372 **LAMICTAL XR can have other serious side effects.** For more information ask your
1373 healthcare provider or pharmacist. Tell your healthcare provider if you have any side effect
1374 that bothers you. Be sure to read the section below entitled “What are the possible side
1375 effects of LAMICTAL XR?”

1376 **4. Patients prescribed LAMICTAL have sometimes been given the wrong medicine**
1377 **because many medicines have names similar to LAMICTAL, so always check that you**
1378 **receive LAMICTAL XR.**

1379 Taking the wrong medication can cause serious health problems. When your healthcare
1380 provider gives you a prescription for LAMICTAL XR:

- 1381
- 1382 • Make sure you can read it clearly.
 - 1383 • Talk to your pharmacist to check that you are given the correct medicine.
 - 1384 • Each time you fill your prescription, check the tablets you receive against the pictures of
the tablets below.

1385 These pictures show the distinct wording, colors, and shapes of the tablets that help to
1386 identify the right strength of LAMICTAL XR. Immediately call your pharmacist if you
1387 receive a LAMICTAL XR tablet that does not look like one of the tablets shown below, as
1388 you may have received the wrong medication.

1389

1390

LAMICTAL XR (lamotrigine) Extended-Release Tablets

 25 mg, yellow with white center Imprinted with LAMICTAL XR 25	 50 mg, green with white center Imprinted with LAMICTAL XR 50	 100 mg, orange with white center Imprinted with LAMICTAL XR 100
 200 mg, blue with white center Imprinted with LAMICTAL XR 200	 300 mg, gray with white center Imprinted with LAMICTAL XR 300	

1391

1392 **What is LAMICTAL XR?**

1393 LAMICTAL XR is a prescription medicine used:

- 1394
- 1395 • together with other medicines to treat primary generalized tonic-clonic seizures and partial
onset seizures in people 13 years of age and older.
 - 1396 • alone to treat partial seizures when changing from certain other medicines used in people 13
1397 years and older. It is not known if LAMICTAL XR is safe or effective in children less than
1398 13 years of age. Other forms of lamotrigine can be used in children aged 2 to 12 years.

1399

1400 **Who should not take LAMICTAL XR?**

1401 You should not take LAMICTAL XR if you have had an allergic reaction to lamotrigine or to
1402 any of the inactive ingredients in LAMICTAL XR. See the end of this leaflet for a complete list
1403 of ingredients in LAMICTAL XR.

1404

1405 **What should I tell my healthcare provider before taking LAMICTAL XR?**

1406 Before taking LAMICTAL XR, tell your healthcare provider about all of your medical
1407 conditions, including if you:

- 1408 • have had a rash or allergic reaction to another antiseizure medicine.
- 1409 • have or have had depression, mood problems, or suicidal thoughts or behavior.
- 1410 • are taking oral contraceptives (birth control pills) or other female hormonal medicines. Do
1411 not start or stop taking birth control pills or other female hormonal medicine until you have
1412 talked with your healthcare provider. Tell your healthcare provider if you have any changes
1413 in your menstrual pattern such as breakthrough bleeding. Stopping these medicines may
1414 cause side effects (such as dizziness, lack of coordination, or double vision). Starting these
1415 medicines may lessen how well LAMICTAL XR works.
- 1416 • are pregnant or plan to become pregnant. It is not known if LAMICTAL XR will harm your
1417 unborn baby. If you become pregnant while taking LAMICTAL XR, talk to your healthcare
1418 provider about registering with the North American Antiepileptic Drug Pregnancy Registry.
1419 You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to
1420 collect information about the safety of antiepileptic drugs during pregnancy.
- 1421 • are breastfeeding. LAMICTAL XR can pass into your breast milk. You and your healthcare
1422 provider should decide if you should take LAMICTAL XR or breastfeed. Breastfeeding
1423 while taking LAMICTAL XR is not recommended.

1424 Tell your healthcare provider about all the medicines you take or if you are planning to take a
1425 new medicine, including prescription and non-prescription medicines, vitamins, and herbal
1426 supplements. Using LAMICTAL XR with certain other medicines can affect each other, causing
1427 side effects.

1428

1429 **How should I take LAMICTAL XR?**

- 1430 • Take LAMICTAL XR exactly as prescribed.
- 1431 • Your healthcare provider may change your dose. Do not change your dose without talking to
1432 your healthcare provider.
- 1433 • Do not stop taking LAMICTAL XR without talking to your healthcare provider. Stopping
1434 LAMICTAL XR suddenly may cause serious problems. For example, if you have epilepsy
1435 and you stop taking LAMICTAL XR suddenly, you may get seizures that do not stop. Talk
1436 with your healthcare provider about how to stop LAMICTAL XR slowly.
- 1437 • If you miss a dose of LAMICTAL XR, take it as soon as you remember. If it is almost time
1438 for your next dose, just skip the missed dose. Take the next dose at your regular time. **Do not**
1439 **take 2 doses at the same time.**

- 1440 • You may not feel the full effect of LAMICTAL XR for several weeks.
- 1441 • If you have epilepsy, tell your healthcare provider if your seizures get worse or if you have
- 1442 any new types of seizures.
- 1443 • LAMICTAL XR can be taken with or without food.
- 1444 • Do not chew, crush, or divide LAMICTAL XR.
- 1445 • Swallow LAMICTAL XR tablets whole.
- 1446 • If you have trouble swallowing LAMICTAL XR Tablets, tell your healthcare provider
- 1447 because there may be another form of lamotrigine you can take.
- 1448 • If you receive LAMICTAL XR in a blisterpack, examine the blisterpack before use. Do not
- 1449 use if blisters are torn, broken, or missing.

1450

1451 **What should I avoid while taking LAMICTAL XR?**

- 1452 • Do not drive a car or operate complex, hazardous machinery until you know how
- 1453 LAMICTAL XR affects you.

1454

1455 **What are possible side effects of LAMICTAL XR?**

- 1456 • See “What is the most important information I should know about LAMICTAL XR?”

1457 Common side effects of LAMICTAL XR include:

- 1458 • Dizziness
- 1459 • Tremor
- 1460 • Double vision
- 1461 • Nausea
- 1462 • Vomiting
- 1463 • Trouble with balance and coordination
- 1464 • Anxiety

1465 Other common side effects that have been reported with another form of lamotrigine include

1466 headache, sleepiness, blurred vision, runny nose, and rash.

1467 Tell your healthcare provider about any side effect that bothers you or that does not go away.

1468 These are not all the possible side effects of LAMICTAL XR. For more information, ask your

1469 healthcare provider or pharmacist.

1470 Call your doctor for medical advice about side effects. You may report side effects to FDA at

1471 1-800-FDA-1088.

1472

1473 **How should I store LAMICTAL XR?**

- 1474 • Store LAMICTAL XR at room temperature between 59°F to 86°F (15°C to 30°C).
- 1475 • **Keep LAMICTAL XR and all medicines out of the reach of children.**

1476

1477 **General information about LAMICTAL XR**

1478 Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.
1479 Do not use LAMICTAL XR for a condition for which it was not prescribed. Do not give
1480 LAMICTAL XR to other people, even if they have the same symptoms you have. It may harm
1481 them.

1482 This Medication Guide summarizes the most important information about LAMICTAL XR. If
1483 you would like more information, talk with your healthcare provider. You can ask your
1484 healthcare provider or pharmacist for information about LAMICTAL XR that is written for
1485 healthcare professionals.

1486 For more information, go to www.lamictalxr.com or call 1-888-825-5249.

1487

1488 **What are the ingredients in LAMICTAL XR?**

1489 Active ingredient: Lamotrigine.

1490 Inactive ingredients: glycerol monostearate, hypromellose, lactose monohydrate, magnesium
1491 stearate, methacrylic acid copolymer dispersion, polyethylene glycol 400, polysorbate 80, silicon
1492 dioxide (25-mg and 50-mg tablets only), titanium dioxide, triethyl citrate, iron oxide black (50-
1493 mg and 300-mg tablets only), iron oxide yellow (25-mg, 50-mg, 100-mg tablets only), iron oxide
1494 red (100-mg tablet only), FD&C Blue No. 2 Aluminum Lake (200-mg tablet only). Tablets are
1495 printed with edible black ink.

1496

1497 **This Medication Guide has been approved by the U.S. Food and Drug Administration.**

1498

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1503

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