

**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, 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 of 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 (1)	January 2010
Dosage and Administration (2.2)	January 2010
Warnings and Precautions, Aseptic Meningitis (5.6)	Month Year

**INDICATIONS AND USAGE**

LAMICTAL XR is an antiepileptic drug (AED) indicated as adjunctive therapy for primary generalized tonic-clonic (PGTC) seizures and partial onset seizures with or without secondary generalization in patients  $\geq 13$  years of age. (1.1)

**DOSAGE AND ADMINISTRATION**

- Doses are administered once daily. Dose escalation and maintenance doses are based on concomitant medications. (2.1, 2.2)
- To avoid an increased risk of rash, the recommended initial dose and subsequent dose escalations should not be exceeded. LAMICTAL XR Patient Titration Kits are available for the first 5 weeks of treatment. (2.1, 16)
- For patients being converted 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 to LAMICTAL XR. (2.3)
- Do not restart LAMICTAL XR in patients who discontinued due to rash unless the potential benefits clearly outweigh the risks. (2.1, 5.1)
- Adjustments to maintenance doses will in most cases be required in patients starting or stopping estrogen-containing oral contraceptives. (2.1, 5.8)
- LAMICTAL XR should be discontinued over a period of at least 2 weeks (approximately 50% 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)

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**CONTRAINDICATIONS**

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

**WARNINGS AND PRECAUTIONS**

- Life-threatening serious rash, and/or rash-related death, may result. (Boxed Warning, 5.1)
- Hypersensitivity reaction may be fatal or life-threatening. Early signs of hypersensitivity (e.g., fever, lymphadenopathy) may present without rash; if signs present, patient should be evaluated immediately.
- LAMICTAL XR should be discontinued if alternate etiology for hypersensitivity signs is not found. (5.2)
- Acute multiorgan failure has resulted (some cases fatal). (5.3)
- Blood dyscrasias (e.g., neutropenia, thrombocytopenia, pancytopenia) may result, either with or without an associated hypersensitivity syndrome. (5.4)
- Suicidal behavior and ideation. (5.5)
- Aseptic meningitis reported in pediatric and adult patients. (5.6)
- Medication errors involving LAMICTAL have occurred. In particular, the names LAMICTAL or lamotrigine can be confused with the names of other commonly used medications. Medication errors may also occur between the different formulations of LAMICTAL. (3.2, 5.7, 16, 17.9)

**ADVERSE REACTIONS**

- Most common adverse reactions (treatment difference  $\geq 4\%$ , LAMICTAL XR - Placebo) are dizziness, tremor/intention tremor, vomiting, and diplopia. (6.1)

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

**DRUG INTERACTIONS**

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

**USE IN SPECIFIC POPULATIONS**

- Pediatric use: Safety and effectiveness in patients below the age of 13 have not been established. (8.4)
- Effectiveness of lamotrigine, used as adjunctive treatment for partial seizures, was not demonstrated in a small randomized, double-blind, placebo-controlled, withdrawal study in very young pediatric patients (1 to 24 months). (8.4)
- Hepatic impairment: Dosage adjustments required. (2.1)
- Healthcare professionals can enroll patients in the Lamotrigine Pregnancy Registry (1-800-336-2176). Patients can enroll themselves in the North American Antiepileptic Drug Pregnancy Registry (1-888-233-2334). (8.1)

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

1

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 (2 to 16 years**  
7 **of age) receiving the immediate-release formulation of LAMICTAL as adjunctive therapy**  
8 **for epilepsy and 0.3% (3 per 1,000) in adults on adjunctive therapy for epilepsy. In a**  
9 **prospectively followed cohort of 1,983 pediatric patients (2 to 16 years of age) with epilepsy**  
10 **taking the adjunctive immediate-release formulation of LAMICTAL, there was 1 rash-**  
11 **related death. LAMICTAL XR is not approved for patients under the age of 13 years. In**  
12 **worldwide postmarketing experience, rare cases of toxic epidermal necrolysis and/or rash-**  
13 **related death have been reported in adult and pediatric patients, but their numbers are too**  
14 **few to permit a precise estimate of the rate.**

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

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

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

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

## 38 **1 INDICATIONS AND USAGE**

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  $\geq 13$  years of age.

42 Safety and effectiveness of LAMICTAL XR for use in patients below the age of 13 have  
43 not been established.

## 44 **2 DOSAGE AND ADMINISTRATION**

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

### 47 **2.1 General Dosing Considerations**

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

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

57 LAMICTAL XR Patient Titration Kits provide LAMICTAL XR at doses consistent with  
58 the recommended titration schedule for the first 5 weeks of treatment, based upon concomitant  
59 medications for patients with partial onset seizures and are intended to help reduce the potential  
60 for rash. The use of LAMICTAL XR Patient Titration Kits is recommended for appropriate  
61 patients who are starting or restarting LAMICTAL XR [*see How Supplied/Storage and Handling*  
62 (16)].

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

72 LAMICTAL XR Added to Drugs Known to Induce or Inhibit Glucuronidation: Drugs  
73 other than those listed in the Clinical Pharmacology section [*see Clinical Pharmacology (12.3)*]  
74 have not been systematically evaluated in combination with lamotrigine. Because lamotrigine is  
75 metabolized predominantly by glucuronic acid conjugation, drugs that are known to induce or

76 inhibit glucuronidation may affect the apparent clearance of lamotrigine and doses of  
77 LAMICTAL XR may require adjustment based on clinical response.

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

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

90 ***Adjustments to the Maintenance Dose of LAMICTAL XR In Women Taking***  
91 ***Estrogen-Containing Oral Contraceptives:***

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

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

115 glucuronidation [see *Drug Interactions (7), Clinical Pharmacology (12.3)*], no adjustment to the  
116 dose of LAMICTAL XR should be necessary.

117 **(3) Stopping Estrogen-Containing Oral Contraceptives:** For women not  
118 taking carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin that  
119 induce lamotrigine glucuronidation [see *Drug Interactions (7), Clinical Pharmacology (12.3)*],  
120 the maintenance dose of LAMICTAL XR will in most cases need to be decreased by as much as  
121 50% in order to maintain a consistent lamotrigine plasma level. The decrease in dose of  
122 LAMICTAL XR should not exceed 25% of the total daily dose per week over a 2-week period,  
123 unless clinical response or lamotrigine plasma levels indicate otherwise [see *Clinical*  
124 *Pharmacology (12.3)*]. For women taking LAMICTAL XR in addition to carbamazepine,  
125 phenytoin, phenobarbital, primidone, or other drugs such as rifampin that induce lamotrigine  
126 glucuronidation [see *Drug Interactions (7), Clinical Pharmacology (12.3)*], no adjustment to the  
127 dose of LAMICTAL XR should be necessary.

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

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

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

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

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

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

158 | **2.2 Primary Generalized Tonic-Clonic and Partial Onset Seizures**

159 This section provides specific dosing recommendations for patients  $\geq 13$  years of age.  
 160 Specific dosing recommendations are provided depending upon concomitant AED or other  
 161 concomitant medications.

162  
 163 **Table 1. Escalation Regimen for LAMICTAL XR in Patients  $\geq 13$  Years of Age**

	For Patients TAKING Valproate <sup>a</sup>	For Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone, <sup>b</sup> or Valproate <sup>a</sup>	For Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone <sup>b</sup> and NOT TAKING Valproate <sup>a</sup>
Weeks 1 and 2	25 mg every <i>other</i> day	25 mg 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 <sup>c</sup>	300 to 400 mg every day <sup>c</sup>	400 to 600 mg every day <sup>c</sup>

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

166 <sup>b</sup> These drugs induce lamotrigine glucuronidation and increase clearance [see *Drug Interactions*  
 167 *(7), Clinical Pharmacology (12.3)*]. Other drugs which have similar effects include estrogen-  
 168 containing oral contraceptives [see *Drug Interactions (7), Clinical Pharmacology (12.3)*].

169 Dosing recommendations for oral contraceptives can be found in General Dosing  
 170 Considerations [see *Dosage and Administration (2.1)*]. Patients on rifampin, or other drugs  
 171 that induce lamotrigine glucuronidation and increase clearance, should follow the same dosing  
 172 titration/maintenance regimen as that used with anticonvulsants that have this effect.

173 <sup>c</sup> Dose increases at week 8 or later should not exceed 100 mg daily at weekly intervals.

174  
 175 **2.3 Conversion From Immediate-Release Lamotrigine Tablets to LAMICTAL XR**

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

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

### 185   **3     DOSAGE FORMS AND STRENGTHS**

#### 186   **3.1    Extended-Release Tablets**

187           25 mg, yellow with white center, round, biconvex, film-coated tablets printed with  
188 “LAMICTAL” and “XR 25.”

189           50 mg, green with white center, round, biconvex, film-coated tablets printed with  
190 “LAMICTAL” and “XR 50.”

191           100 mg, orange with white center, round, biconvex, film-coated tablets printed with  
192 “LAMICTAL” and “XR 100.”

193           200 mg, blue with white center, round, biconvex, film-coated tablets printed with  
194 “LAMICTAL” and “XR 200.”

195           300 mg, gray with white center, caplet-shaped, film-coated tablets printed with  
196 “LAMICTAL” and “XR 300.”

#### 197   **3.2    Potential Medication Errors**

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

### 202   **4     CONTRAINDICATIONS**

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

### 205   **5     WARNINGS AND PRECAUTIONS**

#### 206   **5.1    Serious Skin Rashes [*see Boxed Warning*]**

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

211           Pediatric Population: The incidence of serious rash associated with hospitalization and  
212 discontinuation of the immediate-release formulation of LAMICTAL in a prospectively followed  
213 cohort of pediatric patients (2 to 16 years of age) with epilepsy receiving adjunctive therapy with  
214 immediate-release lamotrigine was approximately 0.8% (16 of 1,983). When 14 of these cases  
215 were reviewed by 3 expert dermatologists, there was considerable disagreement as to their proper  
216 classification. To illustrate, one dermatologist considered none of the cases to be Stevens-  
217 Johnson syndrome; another assigned 7 of the 14 to this diagnosis. There was 1 rash-related death  
218 in this 1,983-patient cohort. Additionally, there have been rare cases of toxic epidermal

219 necrolysis with and without permanent sequelae and/or death in US and foreign postmarketing  
220 experience.

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

225 LAMICTAL XR is not approved in patients under the age of 13 years.

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

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

235 There is evidence that the inclusion of valproate in a multidrug regimen increases the risk  
236 of serious, potentially life-threatening rash in adults. Specifically, of 584 patients administered  
237 the immediate-release formulation of LAMICTAL with valproate in epilepsy clinical trials, 6  
238 (1%) were hospitalized in association with rash; in contrast, 4 (0.16%) of 2,398 clinical trial  
239 patients and volunteers administered the immediate-release formulation of LAMICTAL in the  
240 absence of valproate were hospitalized.

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

## 244 **5.2 Hypersensitivity Reactions**

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

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

## 256 **5.3 Acute Multiorgan Failure**

257 Multiorgan failure, which in some cases has been fatal or irreversible, has been observed  
258 in patients receiving the immediate-release formulation of LAMICTAL. Fatalities associated

259 with multiorgan failure and various degrees of hepatic failure have been reported in 2 of 3,796  
260 adult patients and 4 of 2,435 pediatric patients who received the immediate-release formulation  
261 of LAMICTAL in epilepsy clinical trials. Rare fatalities from multiorgan failure have been  
262 reported in compassionate plea and postmarketing use. The majority of these deaths occurred in  
263 association with other serious medical events, including status epilepticus and overwhelming  
264 sepsis, and hantavirus, making it difficult to identify the initial cause.

265 Additionally, 3 patients (a 45-year-old woman, a 3.5-year-old boy, and an 11-year-old  
266 girl) developed multiorgan dysfunction and disseminated intravascular coagulation 9 to 14 days  
267 after the immediate-release formulation of LAMICTAL was added to their AED regimens. Rash  
268 and elevated transaminases were also present in all patients and rhabdomyolysis was noted in 2  
269 patients. Both pediatric patients were receiving concomitant therapy with valproate, while the  
270 adult patient was being treated with carbamazepine and clonazepam. All patients subsequently  
271 recovered with supportive care after treatment with the immediate-release formulation of  
272 LAMICTAL was discontinued.

#### 273 **5.4 Blood Dyscrasias**

274 There have been reports of blood dyscrasias with the immediate-release formulation of  
275 LAMICTAL that may or may not be associated with the hypersensitivity syndrome. These have  
276 included neutropenia, leukopenia, anemia, thrombocytopenia, pancytopenia, and, rarely, aplastic  
277 anemia and pure red cell aplasia.

#### 278 **5.5 Suicidal Behavior and Ideation**

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

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

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

297 The risk of suicidal thoughts or behavior was generally consistent among drugs in the  
298 data analyzed. The finding of increased risk with AEDs of varying mechanism of action and

299 across a range of indications suggests that the risk applies to all AEDs used for any indication.  
300 The risk did not vary substantially by age (5 to 100 years) in the clinical trials analyzed.

301 Table 2 shows absolute and relative risk by indication for all evaluated AEDs.

302

303 **Table 2. 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

304

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

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

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

## 319 **5.6 Aseptic Meningitis**

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

323 Postmarketing cases of aseptic meningitis have been reported in pediatric and adult  
324 patients taking LAMICTAL for various indications. Symptoms upon presentation have included  
325 headache, fever, nausea, vomiting, and nuchal rigidity. Rash, photophobia, myalgia, chills,  
326 altered consciousness, and somnolence were also noted in some cases. Symptoms have been  
327 reported to occur within 1 day to one and a half months following the initiation of treatment. In  
328 most cases, symptoms were reported to resolve after discontinuation of LAMICTAL. Re-  
329 exposure resulted in a rapid return of symptoms (from within 30 minutes to 1 day following re-

330 initiation of treatment) that were frequently more severe. Some of the patients treated with  
331 LAMICTAL who developed aseptic meningitis had underlying diagnoses of systemic lupus  
332 erythematosus or other autoimmune diseases.

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

### 341 **5.7 Potential Medication Errors**

342 Medication errors involving LAMICTAL have occurred. In particular, the names  
343 LAMICTAL or lamotrigine can be confused with the names of other commonly used  
344 medications. Medication errors may also occur between the different formulations of  
345 LAMICTAL. To reduce the potential of medication errors, write and say LAMICTAL XR  
346 clearly. Depictions of the LAMICTAL XR Extended-Release Tablets can be found in the  
347 Medication Guide. Each LAMICTAL XR tablet has a distinct color and white center, and is  
348 printed with “LAMICTAL XR” and the tablet strength. These distinctive features serve to  
349 identify the different presentations of the drug and thus may help reduce the risk of medication  
350 errors. LAMICTAL XR is supplied in round, unit-of-use bottles with orange caps containing 30  
351 tablets. The label on the bottle includes a depiction of the tablets which further communicates to  
352 patients and pharmacists that the medication is LAMICTAL XR and the specific tablet strength  
353 included in the bottle. The unit-of-use bottle with a distinctive orange cap and distinctive bottle  
354 label features serves to identify the different presentations of the drug and thus may help to  
355 reduce the risk of medication errors. To avoid the medication error of using the wrong drug or  
356 formulation, patients should be strongly advised to visually inspect their tablets to verify that  
357 they are LAMICTAL XR each time they fill their prescription.

### 358 **5.8 Concomitant Use With Oral Contraceptives**

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

### 366 **5.9 Withdrawal Seizures**

367 As with other AEDs, LAMICTAL XR should not be abruptly discontinued. In patients  
368 with epilepsy there is a possibility of increasing seizure frequency. Unless safety concerns  
369 require a more rapid withdrawal, the dose of LAMICTAL XR should be tapered over a period of

370 at least 2 weeks (approximately 50% reduction per week) [*see Dosage and Administration*  
371 (2.1)].

### 372 **5.10 Status Epilepticus**

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

### 379 **5.11 Sudden Unexplained Death in Epilepsy (SUDEP)**

380 During the premarketing development of the immediate-release formulation of  
381 LAMICTAL, 20 sudden and unexplained deaths were recorded among a cohort of 4,700 patients  
382 with epilepsy (5,747 patient-years of exposure).

383 Some of these could represent seizure-related deaths in which the seizure was not  
384 observed, e.g., at night. This represents an incidence of 0.0035 deaths per patient-year. Although  
385 this rate exceeds that expected in a healthy population matched for age and sex, it is within the  
386 range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not  
387 receiving lamotrigine (ranging from 0.0005 for the general population of patients with epilepsy,  
388 to 0.004 for a recently studied clinical trial population similar to that in the clinical development  
389 program for immediate-release lamotrigine, to 0.005 for patients with refractory epilepsy).  
390 Consequently, whether these figures are reassuring or suggest concern depends on the  
391 comparability of the populations reported upon to the cohort receiving immediate-release  
392 lamotrigine and the accuracy of the estimates provided. Probably most reassuring is the  
393 similarity of estimated SUDEP rates in patients receiving immediate-release lamotrigine and  
394 those receiving other AEDs, chemically unrelated to each other, that underwent clinical testing in  
395 similar populations. Importantly, that drug is chemically unrelated to lamotrigine. This evidence  
396 suggests, although it certainly does not prove, that the high SUDEP rates reflect population rates,  
397 not a drug effect.

### 398 **5.12 Addition of LAMICTAL XR to a Multidrug Regimen That Includes Valproate**

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

### 401 **5.13 Binding in the Eye and Other Melanin-Containing Tissues**

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

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

#### 411 **5.14 Laboratory Tests**

412 The value of monitoring plasma concentrations of lamotrigine in patients treated with  
413 LAMICTAL XR has not been established. Because of the possible pharmacokinetic interactions  
414 between lamotrigine and other drugs including AEDs (see Table 4), monitoring of the plasma  
415 levels of lamotrigine and concomitant drugs may be indicated, particularly during dosage  
416 adjustments. In general, clinical judgment should be exercised regarding monitoring of plasma  
417 levels of lamotrigine and other drugs and whether or not dosage adjustments are necessary.

418 Treatment with LAMICTAL XR caused an increased incidence of subnormal (below the  
419 reference range) values in some hematology analytes (e.g., total white blood cells, monocytes).  
420 The treatment effect (LAMICTAL XR % - Placebo %) incidence of subnormal counts was 3%  
421 for total white blood cells and 4% for monocytes.

### 422 **6 ADVERSE REACTIONS**

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

- 425 • Serious skin rashes [*see Warnings and Precautions (5.1)*]
- 426 • Hypersensitivity reactions [*see Warnings and Precautions (5.2)*]
- 427 • Acute multiorgan failure [*see Warnings and Precautions (5.3)*]
- 428 • Blood dyscrasias [*see Warnings and Precautions (5.4)*]
- 429 • Suicidal behavior and ideation [*see Warnings and Precautions (5.5)*]
- 430 • Aseptic meningitis [*see Warnings and Precautions (5.6)*]
- 431 • Withdrawal seizures [*see Warnings and Precautions (5.9)*]
- 432 • Status epilepticus [*see Warnings and Precautions (5.10)*]
- 433 • Sudden unexplained death in epilepsy [*see Warnings and Precautions (5.11)*]

#### 434 **6.1 Clinical Trial Experience With LAMICTAL XR for Treatment of PGTC and** 435 **Partial Onset Seizures**

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

439 LAMICTAL XR has been evaluated for safety in patients  $\geq 13$  years of age with PGTC  
440 and partial onset seizures. The most commonly observed adverse reactions ( $\geq 4\%$  for  
441 LAMICTAL XR and more common on drug than placebo) in these 2 double-blind, placebo-  
442 controlled trials of adjunctive therapy with LAMICTAL XR were, in order of decreasing  
443 treatment difference (LAMICTAL XR % - Placebo %) incidence: dizziness, tremor/intention  
444 tremor, vomiting, and diplopia.

445 In these 2 trials, adverse reactions led to withdrawal of 4 (2%) patients in the group  
446 receiving placebo and 10 (5%) patients in the group receiving LAMICTAL XR. Dizziness was

447 the most common reason for withdrawal in the group receiving LAMICTAL XR (5 patients  
 448 [3%]). The next most common adverse reactions leading to withdrawal in 2 patients each (1%)  
 449 were rash, headache, nausea, and nystagmus.

450 Table 3 displays the incidence of adverse reactions in these two 19-week, double-blind,  
 451 placebo-controlled studies of patients with PGTC and partial onset seizures.

452  
 453 **Table 3. Treatment-Emergent Adverse Reaction Incidence in Double-Blind, Placebo-**  
 454 **Controlled Adjunctive Trials of Patients With Epilepsy (Adverse Reactions  $\geq$ 2% of**  
 455 **Patients Treated With LAMICTAL XR and Numerically More Frequent Than in the**  
 456 **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

457 Note: In these trials the incidence of nonserious rash was 2% for LAMICTAL XR and 3% for  
 458 placebo. In clinical trials evaluating the immediate-release formulation of LAMICTAL, the rate  
 459 of serious rash was 0.3% in adults on adjunctive therapy for epilepsy [see *Boxed Warning*].  
 460

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

464 The incidence for many adverse reactions caused by LAMICTAL XR treatment was  
 465 increased relative to placebo (i.e., LAMICTAL XR % - Placebo % = treatment difference  $\geq 2\%$ )  
 466 in either the titration or maintenance phases of the study. During the titration phase, an increased  
 467 incidence (shown in descending order of % treatment difference) was observed for diarrhea,  
 468 nausea, vomiting, somnolence, vertigo, myalgia, hot flush, and anxiety. During the maintenance  
 469 phase, an increased incidence was observed for dizziness, tremor, and diplopia. Some adverse  
 470 reactions developing in the titration phase were notable for persisting (>7 days) into the  
 471 maintenance phase. These “persistent” adverse reactions included somnolence and dizziness.

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

480 There were insufficient data to evaluate the effect of gender, age, and race on the adverse  
 481 reaction profile for LAMICTAL XR.

482 **6.2 Other Adverse Reactions Observed During the Clinical Development of the**  
 483 **Immediate-Release Formulation of LAMICTAL**

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

487 Adjunctive Therapy in Adults With Epilepsy: In addition to the adverse reactions  
 488 reported above from the development of LAMICTAL XR, the following adverse reactions with

489 an uncertain relationship to lamotrigine were reported during the clinical development of the  
490 immediate-release formulation of LAMICTAL for treatment of epilepsy in adults. These  
491 reactions occurred in  $\geq 2\%$  of patients receiving the immediate-release formulation of  
492 LAMICTAL and more frequently than in the placebo group.

493 *Body as a Whole:* Flu syndrome, fever, abdominal pain, neck pain.

494 *Musculoskeletal:* Arthralgia.

495 *Nervous:* Insomnia, convulsion, irritability, speech disorder, concentration  
496 disturbance.

497 *Respiratory:* Rhinitis, pharyngitis, cough increased.

498 *Skin and Appendages:* Rash, pruritus.

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

500 **Other Clinical Trial Experience:** The immediate-release formulation of LAMICTAL  
501 has been administered to 6,694 individuals for whom complete adverse reaction data was  
502 captured during all clinical trials, only some of which were placebo controlled. During these  
503 trials, all adverse reactions were recorded by the clinical investigators using terminology of their  
504 own choosing. To provide a meaningful estimate of the proportion of individuals having adverse  
505 reactions, similar types of reactions were grouped into a smaller number of standardized  
506 categories using modified COSTART dictionary terminology. The frequencies presented  
507 represent the proportion of the 6,694 individuals exposed to LAMICTAL who experienced an  
508 event of the type cited on at least one occasion while receiving LAMICTAL.

509 Adverse reactions are further classified within body system categories and enumerated in  
510 order of decreasing frequency using the following definitions: *frequent* adverse reactions are  
511 defined as those occurring in at least 1/100 patients; *infrequent* adverse reactions are those  
512 occurring in 1/100 to 1/1,000 patients; *rare* adverse reactions are those occurring in fewer than  
513 1/1,000 patients.

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

515 **Cardiovascular System:** *Infrequent:* Flushing, hypertension, palpitations, postural  
516 hypotension, syncope, tachycardia, and vasodilation.

517 **Dermatological:** *Infrequent:* Acne, hirsutism, maculopapular rash, skin discoloration,  
518 and urticaria. *Rare:* Angioedema, erythema, exfoliative dermatitis, fungal dermatitis, herpes  
519 zoster, leukoderma, multiforme erythema, petechial rash, pustular rash, Stevens-Johnson  
520 syndrome, and vesiculobullous rash.

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

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

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

529 Metabolic and Nutritional Disorders: *Infrequent:* Aspartate transaminase increased.

530 *Rare:* Alcohol intolerance, alkaline phosphatase increase, alanine transaminase increase,  
531 bilirubinemia, general edema, gamma glutamyl transpeptidase increase, and hyperglycemia.

532 Musculoskeletal System: *Infrequent:* Arthritis, leg cramps, myasthenia, and twitching.

533 *Rare:* Bursitis, muscle atrophy, pathological fracture, and tendinous contracture.

534 Nervous System: *Frequent:* Confusion and paresthesia. *Infrequent:* Akathisia, apathy,  
535 aphasia, CNS depression, depersonalization, dysarthria, dyskinesia, euphoria, hallucinations,  
536 hostility, hyperkinesia, hypertonia, libido decreased, memory decrease, mind racing, movement  
537 disorder, myoclonus, panic attack, paranoid reaction, personality disorder, psychosis, stupor, and  
538 suicidal ideation. *Rare:* Choreoathetosis, delirium, delusions, dysphoria, dystonia,  
539 extrapyramidal syndrome, faintness, grand mal convulsions, hemiplegia, hyperalgesia,  
540 hyperesthesia, hypokinesia, hypotonia, manic depression reaction, muscle spasm, neuralgia,  
541 neurosis, paralysis, and peripheral neuritis.

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

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

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

### 551 **6.3 Postmarketing Experience with the Immediate-Release Formulation of** 552 **LAMICTAL**

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

558 Blood and Lymphatic: Agranulocytosis, hemolytic anemia

559 Gastrointestinal: Esophagitis.

560 Hepatobiliary Tract and Pancreas: Pancreatitis.

561 Immunologic: Lupus-like reaction, vasculitis.

562 Lower Respiratory: Apnea.

563 Musculoskeletal: Rhabdomyolysis has been observed in patients experiencing  
564 hypersensitivity reactions.

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

567 Non-site Specific: Progressive immunosuppression.

568 **7 DRUG INTERACTIONS**

569 Significant drug interactions with lamotrigine are summarized in Table 4. Additional  
 570 details of these drug interaction studies, which were conducted using the immediate-release  
 571 formulation of LAMICTAL, are provided in the Clinical Pharmacology section [see *Clinical*  
 572 *Pharmacology (12.3)*].

573

574 **Table 4. 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	Decreased lamotrigine levels approximately 50%.
	↓ levonorgestrel	Decrease in levonorgestrel component by 19%.
Carbamazepine (CBZ) and CBZ epoxide	↓ lamotrigine	Addition of carbamazepine decreases lamotrigine concentration approximately 40%.
	? CBZ epoxide	May increase CBZ epoxide levels.
Phenobarbital/Primidone	↓ lamotrigine	Decreased lamotrigine concentration approximately 40%.
Phenytoin (PHT)	↓ lamotrigine	Decreased lamotrigine concentration approximately 40%.
Rifampin	↓ lamotrigine	Decreased lamotrigine AUC approximately 40%.
Valproate	↑ lamotrigine	Increased lamotrigine concentrations slightly more than 2-fold.
	? valproate	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.

575 ↓ = Decreased (induces lamotrigine glucuronidation).

576 ↑ = Increased (inhibits lamotrigine glucuronidation).

577 ? = Conflicting data.

## 578 **8 USE IN SPECIFIC POPULATIONS**

### 579 **8.1 Pregnancy**

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

589 A behavioral teratology study was conducted in rats dosed during the period of  
590 organogenesis. At day 21 postpartum, offspring of dams receiving 5 mg/kg/day or higher  
591 displayed a significantly longer latent period for open field exploration and a lower frequency of  
592 rearing. In a swimming maze test performed on days 39 to 44 postpartum, time to completion  
593 was increased in offspring of dams receiving 25 mg/kg/day. These doses represent 0.1 and 0.5  
594 times the clinical dose on a mg/m<sup>2</sup> basis, respectively.

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

598 When pregnant rats were orally dosed at 0.1, 0.14, or 0.3 times the highest human  
599 maintenance dose (on a mg/m<sup>2</sup> basis) during the latter part of gestation (days 15 to 20), maternal  
600 toxicity and fetal death were seen. In dams, food consumption and weight gain were reduced,  
601 and the gestation period was slightly prolonged (22.6 vs. 22.0 days in the control group).  
602 Stillborn pups were found in all 3 drug-treated groups with the highest number in the high-dose  
603 group. Postnatal death was also seen, but only in the 2 highest doses, and occurred between days  
604 1 and 20. Some of these deaths appear to be drug-related and not secondary to the maternal  
605 toxicity. A no-observed-effect level (NOEL) could not be determined for this study.

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

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

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

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

## 627 **8.2 Labor and Delivery**

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

## 629 **8.3 Nursing Mothers**

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

## 633 **8.4 Pediatric Use**

634 LAMICTAL XR is indicated as adjunctive therapy for PGTC and partial onset seizures  
635 with or without secondary generalization in patients  $\geq 13$  years of age. Safety and effectiveness of  
636 LAMICTAL XR for any use in patients below the age of 13 have not been established.

637 The immediate-release formulation of LAMICTAL is indicated for adjunctive therapy in  
638 patients  $\geq 2$  years of age for partial seizures, the generalized seizures of Lennox-Gastaut  
639 syndrome, and primary generalized tonic-clonic seizures.

640 Safety and efficacy of the immediate-release formulation of LAMICTAL, used as  
641 adjunctive treatment for partial seizures, were not demonstrated in a small randomized, double-  
642 blind, placebo-controlled, withdrawal study in very young pediatric patients (1 to 24 months).  
643 The immediate-release formulation of LAMICTAL was associated with an increased risk for  
644 infectious adverse reactions (LAMICTAL 37%, Placebo 5%), and respiratory adverse reactions  
645 (LAMICTAL 26%, Placebo 5%). Infectious adverse reactions included bronchiolitis, bronchitis,  
646 ear infection, eye infection, otitis externa, pharyngitis, urinary tract infection, and viral infection.  
647 Respiratory adverse reactions included nasal congestion, cough, and apnea.

## 648 **8.5 Geriatric Use**

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

## 655 **8.6 Patients With Hepatic Impairment**

656 Experience in patients with hepatic impairment is limited. Based on a clinical  
657 pharmacology study with the immediate-release formulation of LAMICTAL in 24 patients with  
658 mild, moderate, and severe liver impairment [see *Clinical Pharmacology (12.3)*], the following  
659 general recommendations can be made. No dosage adjustment is needed in patients with mild  
660 liver impairment. Initial, escalation, and maintenance doses should generally be reduced by  
661 approximately 25% in patients with moderate and severe liver impairment without ascites and  
662 50% in patients with severe liver impairment with ascites. Escalation and maintenance doses  
663 may be adjusted according to clinical response [see *Dosage and Administration (2.1)*].

## 664 **8.7 Patients With Renal Impairment**

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

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

## 675 **10 OVERDOSAGE**

### 676 **10.1 Human Overdose Experience**

677 Overdoses involving quantities up to 15 g have been reported for the immediate-release  
678 formulation of LAMICTAL, some of which have been fatal. Overdose has resulted in ataxia,  
679 nystagmus, increased seizures, decreased level of consciousness, coma, and intraventricular  
680 conduction delay.

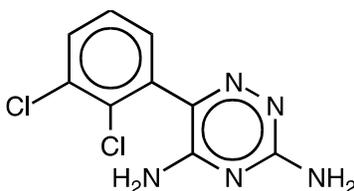
### 681 **10.2 Management of Overdose**

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

## 690 **11 DESCRIPTION**

691 LAMICTAL XR (lamotrigine), an AED of the phenyltriazine class, is chemically  
692 unrelated to existing AEDs. Its chemical name is 3,5-diamino-6-(2,3-dichlorophenyl)-*as*-triazine,  
693 its molecular formula is C<sub>9</sub>H<sub>7</sub>N<sub>5</sub>Cl<sub>2</sub>, and its molecular weight is 256.09. Lamotrigine is a white to  
694 pale cream-colored powder and has a pK<sub>a</sub> of 5.7. Lamotrigine is very slightly soluble in water

695 (0.17 mg/mL at 25°C) and slightly soluble in 0.1 M HCl (4.1 mg/mL at 25°C). The structural  
696 formula is:  
697



698  
699  
700 LAMICTAL XR Extended-Release Tablets are supplied for oral administration as 25-mg  
701 (yellow with white center), 50-mg (green with white center), 100-mg (orange with white center),  
702 200-mg (blue with white center), and 300-mg (gray with white center) tablets. Each tablet  
703 contains the labeled amount of lamotrigine and the following inactive ingredients: glycerol  
704 monostearate, hypromellose, lactose monohydrate; magnesium stearate; methacrylic acid  
705 copolymer dispersion, polyethylene glycol 400, polysorbate 80, silicon dioxide (25-mg and 50-  
706 mg tablets only), titanium dioxide, triethyl citrate, iron oxide black (50-mg and 300-mg tablets  
707 only), iron oxide yellow (25-mg, 50-mg, 100-mg tablets only), iron oxide red (100-mg tablet  
708 only), FD&C Blue No. 2 Aluminum Lake (200-mg tablet only). Tablets are printed with edible  
709 black ink.

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

## 716 12 CLINICAL PHARMACOLOGY

### 717 12.1 Mechanism of Action

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

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

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

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

740 Lamotrigine did not inhibit N-methyl d-aspartate (NMDA)-induced depolarizations in rat cortical  
741 slices or NMDA-induced cyclic GMP formation in immature rat cerebellum, nor did lamotrigine  
742 displace compounds that are either competitive or noncompetitive ligands at this glutamate  
743 receptor complex (CNQX, CGS, TCHP). The IC<sub>50</sub> for lamotrigine effects on NMDA-induced  
744 currents (in the presence of 3 μM of glycine) in cultured hippocampal neurons exceeded  
745 100 μM.

## 746 **12.2 Pharmacodynamics**

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

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

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

761 Cardiovascular: In dogs, lamotrigine is extensively metabolized to a 2-N-methyl  
762 metabolite. This metabolite causes dose-dependent prolongations of the PR interval, widening of  
763 the QRS complex, and, at higher doses, complete AV conduction block. Similar cardiovascular  
764 effects are not anticipated in humans because only trace amounts of the 2-N-methyl metabolite  
765 (<0.6% of lamotrigine dose) have been found in human urine [see *Clinical Pharmacology*  
766 *(12.3)*]. However, it is conceivable that plasma concentrations of this metabolite could be  
767 increased in patients with a reduced capacity to glucuronidate lamotrigine (e.g., in patients with  
768 liver disease).

## 769 **12.3 Pharmacokinetics**

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

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

776 In an open-label, crossover study of 44 subjects with epilepsy receiving concomitant  
777 AEDs, the steady-state pharmacokinetics of lamotrigine were compared following administration  
778 of equivalent total doses of LAMICTAL XR given once daily with those of lamotrigine  
779 immediate-release given twice daily. In this study, the median time to peak concentration ( $T_{max}$ )  
780 following administration of LAMICTAL XR was 4 to 6 hours in patients taking carbamazepine,  
781 phenytoin, phenobarbital, or primidone; 9 to 11 hours in patients taking VPA; and 6 to 10 hours  
782 in patients taking AEDs other than carbamazepine, phenytoin, phenobarbital, primidone, or  
783 VPA. In comparison, the median  $T_{max}$  following administration of immediate-release lamotrigine  
784 was between 1 and 1.5 hours.

785 The steady-state trough concentrations for extended-release lamotrigine were similar to  
786 or higher than those of immediate-release lamotrigine depending on concomitant AED (Table 5).  
787 A mean reduction in the lamotrigine  $C_{max}$  by 11% to 29% was observed for LAMICTAL XR  
788 compared to immediate-release lamotrigine resulting in a decrease in the peak-to-trough  
789 fluctuation in serum lamotrigine concentrations. However, in some subjects receiving enzyme-  
790 inducing AEDs, a reduction in  $C_{max}$  of 44% to 77% was observed. The degree of fluctuation was  
791 reduced by 17% in patients taking enzyme-inducing AEDs, 34% in patients taking VPA, and  
792 37% in patients taking AEDs other than carbamazepine, phenytoin, phenobarbital, primidone, or  
793 VPA. LAMICTAL XR and immediate-release lamotrigine regimens were similar with respect to  
794 area under the curve (AUC, a measure of the extent of bioavailability) for patients receiving  
795 AEDs other than those known to induce the metabolism of lamotrigine. The relative  
796 bioavailability of extended-release lamotrigine was approximately 21% lower than immediate-  
797 release lamotrigine in subjects receiving enzyme-inducing AEDs. However, in some subjects in  
798 this group a reduction in exposure of up to 70% was observed when switched to  
799 LAMICTAL XR. Therefore, doses may need to be adjusted in some subjects based on  
800 therapeutic response.

801

802 **Table 5. Steady-State Bioavailability of LAMICTAL XR Relative to Immediate-Release**  
803 **Lamotrigine at Equivalent Daily Doses (Ratio of XR to IR 90% CI)**

Concomitant AED	AUC <sub>(0-24ss)</sub>	$C_{max}$	$C_{min}$
EIAEDs <sup>a</sup>	0.79 (0.69, 0.90)	0.71 (0.61, 0.82)	0.99 (0.89, 1.09)
VPA	0.94 (0.81, 1.08)	0.88 (0.75, 1.03)	0.99 (0.88, 1.10)
AEDs other than EIAEDs <sup>a</sup> or VPA	1.00 (0.88, 1.14)	0.89 (0.78, 1.03)	1.14 (1.03, 1.25)

804 <sup>a</sup> EIAEDs include carbamazepine, phenytoin, phenobarbital, and primidone.

805

806 **Dose Proportionality:** In healthy volunteers not receiving any other medications and  
807 given LAMICTAL XR once daily, the systemic exposure to lamotrigine increased in direct  
808 proportion to the dose administered over the range of 50 to 200 mg. At doses between 25 and  
809 50 mg, the increase was less than dose proportional, with a 2-fold increase in dose resulting in an  
810 approximately 1.6-fold increase in systemic exposure.

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

815 **Protein Binding:** Data from in vitro studies indicate that lamotrigine is approximately  
816 55% bound to human plasma proteins at plasma lamotrigine concentrations from 1 to 10 mcg/mL  
817 (10 mcg/mL is 4 to 6 times the trough plasma concentration observed in the controlled efficacy  
818 trials). Because lamotrigine is not highly bound to plasma proteins, clinically significant  
819 interactions with other drugs through competition for protein binding sites are unlikely. The  
820 binding of lamotrigine to plasma proteins did not change in the presence of therapeutic  
821 concentrations of phenytoin, phenobarbital, or valproate. Lamotrigine did not displace other  
822 AEDs (carbamazepine, phenytoin, phenobarbital) from protein-binding sites.

823 **Metabolism:** Lamotrigine is metabolized predominantly by glucuronic acid conjugation;  
824 the major metabolite is an inactive 2-N-glucuronide conjugate. After oral administration of  
825 240 mg of <sup>14</sup>C-lamotrigine (15 μCi) to 6 healthy volunteers, 94% was recovered in the urine and  
826 2% was recovered in the feces. The radioactivity in the urine consisted of unchanged lamotrigine  
827 (10%), the 2-N-glucuronide (76%), a 5-N-glucuronide (10%), a 2-N-methyl metabolite (0.14%),  
828 and other unidentified minor metabolites (4%).

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

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

838 **Elimination:** The elimination half-life and apparent clearance of lamotrigine following  
839 administration of immediate-release lamotrigine to adult patients with epilepsy and healthy  
840 volunteers is summarized in Table 6. Half-life and apparent oral clearance vary depending on  
841 concomitant AEDs.

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

845  
 846  
 847

**Table 6. Mean<sup>a</sup> Pharmacokinetic Parameters of Immediate-Release Lamotrigine in Healthy Volunteers and Adult Patients With Epilepsy**

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

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

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

857  
 858 **Drug Interactions:** The apparent clearance of lamotrigine is affected by the  
 859 coadministration of certain medications [see Warnings and Precautions (5.8, 5.11), Drug  
 860 Interactions (7)].

861 The net effects of drug interactions with lamotrigine are summarized in Table 7. Details  
 862 of the drug interaction studies, which were done using immediate-release lamotrigine, are  
 863 provided following Table 7.

864  
 865 **Table 7. Summary of Drug Interactions With Lamotrigine**

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

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

- 867 <sup>b</sup> Net effects were estimated by comparing the mean clearance values obtained in adjunctive  
868 clinical trials and volunteer studies.
- 869 <sup>c</sup> The effect of other hormonal contraceptive preparations or hormone replacement therapy on  
870 the pharmacokinetics of lamotrigine has not been systematically evaluated in clinical trials,  
871 although the effect may be similar to that seen with the ethinylestradiol/levonorgestrel  
872 combinations.
- 873 <sup>d</sup> Modest decrease in levonorgestrel.
- 874 <sup>e</sup> Not administered, but an active metabolite of carbamazepine.
- 875 <sup>f</sup> Slight decrease, not expected to be clinically relevant.
- 876 <sup>g</sup> Not administered, but an active metabolite of oxcarbazepine.
- 877 <sup>h</sup> Slight increase, not expected to be clinically relevant.
- 878 ↔ = No significant effect.
- 879 ? = Conflicting data.
- 880

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

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

896 In the same study, coadministration of lamotrigine (300 mg/day) in 16 female volunteers  
897 did not affect the pharmacokinetics of the ethinylestradiol component of the oral contraceptive  
898 preparation. There were mean decreases in the AUC and C<sub>max</sub> of the levonorgestrel component of  
899 19% and 12%, respectively. Measurement of serum progesterone indicated that there was no  
900 hormonal evidence of ovulation in any of the 16 volunteers, although measurement of serum  
901 FSH, LH, and estradiol indicated that there was some loss of suppression of the hypothalamic-  
902 pituitary-ovarian axis.

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

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

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

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

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

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

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

928 The addition of carbamazepine decreases lamotrigine steady-state concentrations by  
929 approximately 40%.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

978 Valproate: When lamotrigine was administered to healthy volunteers ( $n = 18$ ) receiving  
979 valproate, the trough steady-state valproate plasma concentrations decreased by an average of  
980 25% over a 3-week period, and then stabilized. However, adding lamotrigine to the existing  
981 therapy did not cause a change in valproate plasma concentrations in either adult or pediatric  
982 patients in controlled clinical trials.

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

987            **Zonisamide:** In a study of 18 patients with epilepsy, coadministration of zonisamide  
988 (200 to 400 mg/day) with lamotrigine (150 to 500 mg/day for 35 days) had no significant effect  
989 on the pharmacokinetics of lamotrigine.

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

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

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

1000           **Special Populations: Patients With Renal Impairment:** Twelve volunteers with  
1001 chronic renal failure (mean creatinine clearance: 13 mL/min; range: 6 to 23) and another  
1002 6 individuals undergoing hemodialysis were each given a single 100 mg dose of immediate-  
1003 release lamotrigine. The mean plasma half-lives determined in the study were 42.9 hours  
1004 (chronic renal failure), 13.0 hours (during hemodialysis), and 57.4 hours (between hemodialysis)  
1005 compared with 26.2 hours in healthy volunteers. On average, approximately 20% (range: 5.6 to  
1006 35.1) of the amount of lamotrigine present in the body was eliminated by hemodialysis during a  
1007 4-hour session [*see Dosage and Administration (2.1)*].

1008           **Hepatic Disease:** The pharmacokinetics of lamotrigine following a single 100-mg  
1009 dose of immediate-release lamotrigine were evaluated in 24 subjects with mild, moderate, and  
1010 severe hepatic impairment (Child-Pugh Classification system) and compared with 12 subjects  
1011 without hepatic impairment. The patients with severe hepatic impairment were without ascites  
1012 (n = 2) or with ascites (n = 5). The mean apparent clearances of lamotrigine in patients with mild  
1013 (n = 12), moderate (n = 5), severe without ascites (n = 2), and severe with ascites (n = 5) liver  
1014 impairment were  $0.30 \pm 0.09$ ,  $0.24 \pm 0.1$ ,  $0.21 \pm 0.04$ , and  $0.15 \pm 0.09$  mL/min/kg, respectively,  
1015 as compared with  $0.37 \pm 0.1$  mL/min/kg in the healthy controls. Mean half-lives of lamotrigine  
1016 in patients with mild, moderate, severe without ascites, and severe with ascites hepatic  
1017 impairment were  $46 \pm 20$ ,  $72 \pm 44$ ,  $67 \pm 11$ , and  $100 \pm 48$  hours, respectively, as compared with  
1018  $33 \pm 7$  hours in healthy controls [*see Dosage and Administration (2.1)*].

1019           **Elderly:** The pharmacokinetics of lamotrigine following a single 150 mg dose of  
1020 immediate-release lamotrigine were evaluated in 12 elderly volunteers between the ages of 65  
1021 and 76 years (mean creatinine clearance: 61 mL/min, range: 33 to 108 mL/min). The mean half-  
1022 life of lamotrigine in these subjects was 31.2 hours (range: 24.5 to 43.4 hours), and the mean  
1023 clearance was 0.40 mL/min/kg (range: 0.26 to 0.48 mL/min/kg).

1024           **Gender:** The clearance of lamotrigine is not affected by gender. However, during  
1025 dose escalation of immediate-release lamotrigine in one clinical trial in patients with epilepsy on

1026 a stable dose of valproate (n = 77), mean trough lamotrigine concentrations, unadjusted for  
1027 weight, were 24% to 45% higher (0.3 to 1.7 mcg/mL) in females than in males.

1028 *Race:* The apparent oral clearance of lamotrigine was 25% lower in non-Caucasians  
1029 than Caucasians.

1030 *Pediatric Patients:* Safety and effectiveness of LAMICTAL XR for use in patients  
1031 below the age of 13 have not been established.

## 1032 **13 NONCLINICAL TOXICOLOGY**

### 1033 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

1034 No evidence of carcinogenicity was seen in 1 mouse study or 2 rat studies following oral  
1035 administration of lamotrigine for up to 2 years at maximum tolerated doses (30 mg/kg/day for  
1036 mice and 10 to 15 mg/kg/day for rats, doses that are equivalent to 90 mg/m<sup>2</sup> and 60 to 90 mg/m<sup>2</sup>,  
1037 respectively). Steady-state plasma concentrations ranged from 1 to 4 mcg/mL in the mouse study  
1038 and 1 to 10 mcg/mL in the rat study. Plasma concentrations associated with the recommended  
1039 human doses of 300 to 500 mg/day are generally in the range of 2 to 5 mcg/mL, but  
1040 concentrations as high as 19 mcg/mL have been recorded.

1041 Lamotrigine was not mutagenic in the presence or absence of metabolic activation when  
1042 tested in 2 gene mutation assays (the Ames test and the in vitro mammalian mouse lymphoma  
1043 assay). In 2 cytogenetic assays (the in vitro human lymphocyte assay and the in vivo rat bone  
1044 marrow assay), lamotrigine did not increase the incidence of structural or numerical  
1045 chromosomal abnormalities.

1046 No evidence of impairment of fertility was detected in rats given oral doses of  
1047 lamotrigine up to 2.4 times the highest usual human maintenance dose of 8.33 mg/kg/day or  
1048 0.4 times the human dose on a mg/m<sup>2</sup> basis. The effect of lamotrigine on human fertility is  
1049 unknown.

## 1050 **14 CLINICAL STUDIES**

### 1051 **14.1 PGTC Seizures**

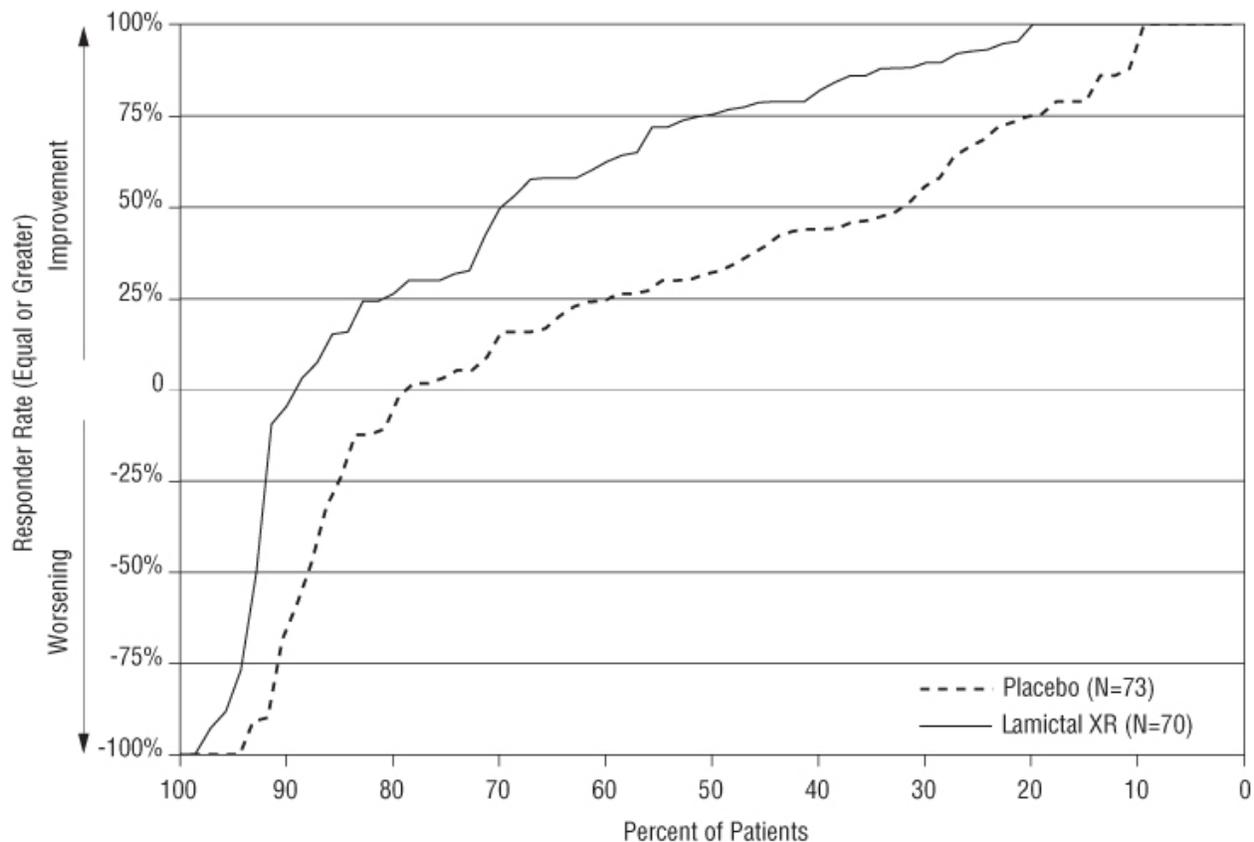
1052 The effectiveness of LAMICTAL XR as adjunctive therapy was established in PGTC  
1053 seizures in a 19-week, international, multicenter, double-blind, randomized, placebo-controlled  
1054 study in 143 patients 13 years of age and older (n = 70 on LAMICTAL XR and n = 73 on  
1055 placebo). Patients with at least 3 PGTC seizures during an 8-week baseline phase were  
1056 randomized to 19 weeks of treatment with LAMICTAL XR or placebo added to their current  
1057 AED regimen of up to 2 drugs. Patients were dosed on a fixed-dose regimen, with target doses  
1058 ranging from 200 mg/day to 500 mg/day of LAMICTAL XR based on concomitant AED(s)  
1059 (target dose = 200 mg for valproate, 300 mg for AEDs not altering plasma lamotrigine levels,  
1060 and 500 mg for enzyme-inducing AEDs).

1061 The primary efficacy endpoint was percent change from baseline in PGTC seizure  
1062 frequency during the double-blind treatment phase. For the intent-to-treat population, the median  
1063 percent reduction in PGTC seizure frequency was 75% in patients treated with LAMICTAL XR

1064 and 32% in patients treated with placebo, a difference that was statistically significant, defined as  
1065 a 2-sided  $p$  value  $\leq 0.05$ .

1066 Figure 1 presents the percentage of patients (X-axis) with a percent reduction in PGTC  
1067 seizure frequency (responder rate) from baseline through the entire treatment period at least as  
1068 great as that represented on the Y-axis. A positive value on the Y-axis indicates an improvement  
1069 from baseline (i.e., a decrease in seizure frequency), while a negative value indicates a worsening  
1070 from baseline (i.e., an increase in seizure frequency). Thus, in a display of this type, a curve for  
1071 an effective treatment is shifted to the left of the curve for placebo. The proportion of patients  
1072 achieving any particular level of reduction in PGTC seizure frequency was consistently higher  
1073 for the group treated with LAMICTAL XR compared with the placebo group. For example, 70%  
1074 of patients randomized to LAMICTAL XR experienced a 50% or greater reduction in PGTC  
1075 seizure frequency, compared with 32% of patients randomized to placebo. Patients with an  
1076 increase in seizure frequency  $>100\%$  are represented on the Y-axis as equal to or greater than  
1077  $-100\%$ .

1078  
1079 **Figure 1. Proportion of Patients by Responder Rate for LAMICTAL XR and Placebo Group**  
1080 **(PGTC Study)**



1081

1082 **14.2 Partial Onset Seizures**

1083           The effectiveness of immediate-release lamotrigine as adjunctive therapy was initially  
1084 established in 3 pivotal multicenter, placebo-controlled, double-blind clinical trials in 355 adults  
1085 with refractory partial onset seizures.

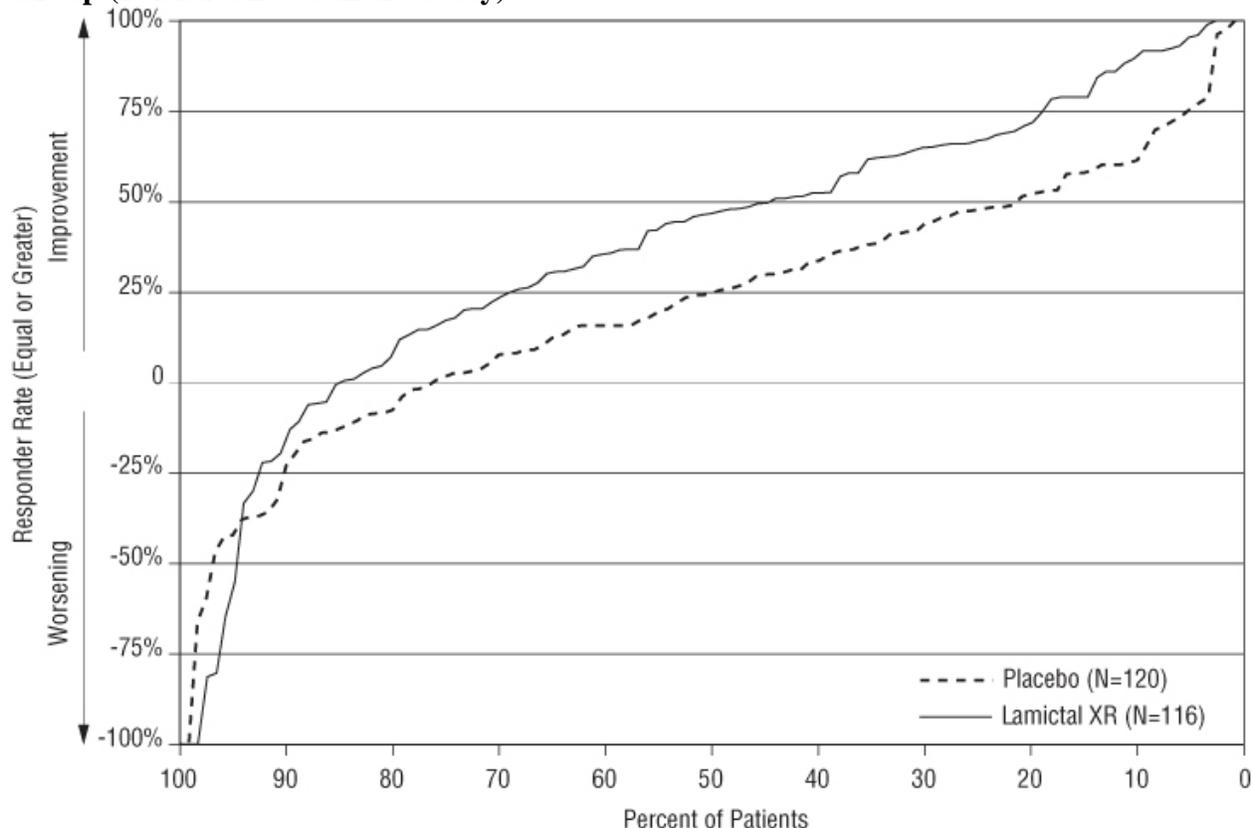
1086           The effectiveness of LAMICTAL XR as adjunctive therapy in partial onset seizures, with  
1087 or without secondary generalization, was established in a 19-week, multicenter, double-blind,  
1088 placebo-controlled trial in 236 patients, 13 years of age and older (approximately 93% of patients  
1089 were 16 to 65 years old). Approximately 36% were from the U.S. and approximately 64% were  
1090 from other countries including Argentina, Brazil, Chile, Germany, India, Korea, Russian  
1091 Federation, and Ukraine. Patients with at least 8 partial onset seizures during an 8-week  
1092 prospective baseline phase (or 4-week prospective baseline coupled with a 4-week historical  
1093 baseline documented with seizure diary data) were randomized to treatment with  
1094 LAMICTAL XR (n = 116) or placebo (n = 120) added to their current regimen of 1 or 2 AEDs.  
1095 Approximately half of the patients were taking 2 concomitant AEDs at baseline. Target doses  
1096 ranged from 200 to 500 mg/day of LAMICTAL XR based on concomitant AED (target dose =  
1097 200 mg for valproate, 300 mg for AEDs not altering plasma lamotrigine, and 500 mg for  
1098 enzyme-inducing AEDs). The median partial seizure frequency per week at baseline was 2.3 for  
1099 LAMICTAL XR and 2.1 for placebo.

1100           The primary endpoint was the median percent change from baseline in partial onset  
1101 seizure frequency during the entire double-blind treatment phase. The median percent reductions  
1102 in weekly partial onset seizures were 47% in patients treated with LAMICTAL XR and 25% on  
1103 placebo, a difference that was statistically significant, defined as a 2-sided *p* value  $\leq 0.05$ .

1104           Figure 2 presents the percentage of patients (X-axis) with a percent reduction in partial  
1105 seizure frequency (responder rate) from baseline through the entire treatment period at least as  
1106 great as that represented on the Y-axis. The proportion of patients achieving any particular level  
1107 of reduction in partial seizure frequency was consistently higher for the group treated with  
1108 LAMICTAL XR compared with the placebo group. For example, 44% of patients randomized to  
1109 LAMICTAL XR experienced a 50% or greater reduction in partial seizure frequency, compared  
1110 with 21% of patients randomized to placebo.

1111

1112 **Figure 2. Proportion of Patients by Responder Rate for LAMICTAL XR and Placebo**  
1113 **Group (Partial Onset Seizure Study)**



1114  
1115

## 1116 **16 HOW SUPPLIED/STORAGE AND HANDLING**

### 1117 **LAMICTAL XR (lamotrigine) Extended-Release Tablets**

1118 25 mg, yellow with a white center, round, biconvex, film-coated tablets printed on one  
1119 face in black ink with “LAMICTAL” and “XR 25”, unit-of-use bottles of 30 with orange caps  
1120 (NDC 0173-0754-00).

1121 50 mg, green with a white center, round, biconvex, film-coated tablets printed on one  
1122 face in black ink with “LAMICTAL” and “XR 50”, unit-of-use bottles of 30 with orange caps  
1123 (NDC 0173-0755-00).

1124 100 mg, orange with a white center, round, biconvex, film-coated tablets printed on one  
1125 face in black ink with “LAMICTAL” and “XR 100”, unit-of-use bottles of 30 with orange caps  
1126 (NDC 0173-0756-00).

1127 200 mg, blue with a white center, round, biconvex, film-coated tablets printed on one  
1128 face in black ink with “LAMICTAL” and “XR 200”, unit-of-use bottles of 30 with orange caps  
1129 (NDC 0173-0757-00).

1130 300 mg, gray with a white center, caplet-shaped, film-coated tablets printed on one face  
1131 in black ink with “LAMICTAL” and “XR 300”, unit-of-use bottles of 30 with orange caps (NDC  
1132 0173-0761-00).

1133 **LAMICTAL XR (lamotrigine) Patient Titration Kit for Patients Taking Valproate**  
1134 **(Blue XR Kit)**

1135 25 mg, yellow with a white center, round, biconvex, film-coated tablets printed on one  
1136 face in black ink with “LAMICTAL” and “XR 25” and 50 mg, green with a white center, round,  
1137 biconvex, film-coated tablets printed on one face in black ink with “LAMICTAL” and “XR 50”;  
1138 blisterpack of 21/25-mg tablets and 7/50-mg tablets (NDC 0173-0758-00).

1139 **LAMICTAL XR (lamotrigine) Patient Titration Kit for Patients Taking**  
1140 **Carbamazepine, Phenytoin, Phenobarbital, or Primidone, and Not Taking Valproate**  
1141 **(Green XR Kit)**

1142 50 mg, green with a white center, round, biconvex, film-coated tablets printed on one  
1143 face in black ink with “LAMICTAL” and “XR 50”; 100 mg, orange with a white center, round,  
1144 biconvex, film-coated tablets printed on one face in black ink with “LAMICTAL” and “XR  
1145 100”; and 200 mg, blue with a white center, round, biconvex, film-coated tablets printed on one  
1146 face in black ink with “LAMICTAL” and “XR 200”; blisterpack of 14/50-mg tablets, 14/100-mg  
1147 tablets, and 7/200-mg tablets (NDC 0173-0759-00).

1148 **LAMICTAL XR (lamotrigine) Patient Titration Kit for Patients Not Taking**  
1149 **Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate (Orange XR Kit)**

1150 25 mg, yellow with a white center, round, biconvex, film-coated tablets printed on one  
1151 face in black ink with “LAMICTAL” and “XR 25”; 50 mg, green with a white center, round,  
1152 biconvex, film-coated tablets printed on one face in black ink with “LAMICTAL” and “XR 50”;  
1153 and 100 mg, orange with a white center, round, biconvex, film-coated tablets printed on one face  
1154 in black ink with “LAMICTAL” and “XR 100”; blisterpack of 14/25-mg tablets, 14/50-mg  
1155 tablets, and 7/100-mg tablets (NDC 0173-0760-00).

1156 **Storage:** Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP  
1157 Controlled Room Temperature].

1158 **17 PATIENT COUNSELING INFORMATION**

1159 See Medication Guide.

1160 **17.1 Rash**

1161 Prior to initiation of treatment with LAMICTAL XR, the patient should be instructed that  
1162 a rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy) may herald  
1163 a serious medical event and that the patient should report any such occurrence to a physician  
1164 immediately.

1165 **17.2 Suicidal Thinking and Behavior**

1166 Patients, their caregivers, and families should be counseled that AEDs, including  
1167 LAMICTAL XR, may increase the risk of suicidal thoughts and behavior and should be advised  
1168 of the need to be alert for the emergence or worsening of symptoms of depression, any unusual  
1169 changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about  
1170 self-harm. Behaviors of concern should be reported immediately to healthcare providers.

1171 **17.3 Worsening of Seizures**

1172 Patients should be advised to notify their physician if worsening of seizure control  
1173 occurs.

#### 1174 **17.4 CNS Adverse Effects**

1175 Patients should be advised that LAMICTAL XR may cause dizziness, somnolence, and  
1176 other symptoms and signs of central nervous system (CNS) depression. Accordingly, they should  
1177 be advised neither to drive a car nor to operate other complex machinery until they have gained  
1178 sufficient experience on LAMICTAL XR to gauge whether or not it adversely affects their  
1179 mental and/or motor performance.

#### 1180 **17.5 Blood Dyscrasias and/or Acute Multiorgan Failure**

1181 Patients should be advised of the possibility of blood dyscrasias and/or acute multiorgan  
1182 failure and to contact their physician immediately if they experience any signs or symptoms of  
1183 these conditions [*see Warnings and Precautions (5.3, 5.4)*].

#### 1184 **17.6 Pregnancy**

1185 Patients should be advised to notify their physicians if they become pregnant or intend to  
1186 become pregnant during therapy. Patients should be advised to notify their physicians if they  
1187 intend to breastfeed or are breastfeeding an infant.

1188 Patients should also be encouraged to enroll in the NAAED Pregnancy Registry if they  
1189 become pregnant. This registry is collecting information about the safety of antiepileptic drugs  
1190 during pregnancy. To enroll, patients can call the toll-free number 1-888-233-2334 [*see Use in*  
1191 *Specific Populations (8.1)*].

#### 1192 **17.7 Oral Contraceptive Use**

1193 Women should be advised to notify their physician if they plan to start or stop use of oral  
1194 contraceptives or other female hormonal preparations. Starting estrogen-containing oral  
1195 contraceptives may significantly decrease lamotrigine plasma levels and stopping estrogen-  
1196 containing oral contraceptives (including the “pill-free” week) may significantly increase  
1197 lamotrigine plasma levels [*see Warnings and Precautions (5.8), Clinical Pharmacology (12.3)*].  
1198 Women should also be advised to promptly notify their physician if they experience adverse  
1199 reactions or changes in menstrual pattern (e.g., break-through bleeding) while receiving  
1200 LAMICTAL XR in combination with these medications.

#### 1201 **17.8 Discontinuing LAMICTAL XR**

1202 Patients should be advised to notify their physician if they stop taking LAMICTAL XR  
1203 for any reason and not to resume LAMICTAL XR without consulting their physician.

#### 1204 **17.9 Aseptic Meningitis**

1205 Patients should be advised that LAMICTAL XR may cause aseptic meningitis. Patients  
1206 should be advised to notify their physician immediately if they develop signs and symptoms of  
1207 meningitis such as headache, fever, nausea, vomiting, stiff neck, rash, abnormal sensitivity to  
1208 light, myalgia, chills, confusion, or drowsiness while taking LAMICTAL XR.

#### 1209 **17.10 Potential Medication Errors**

1210 Medication errors involving LAMICTAL have occurred. In particular the names  
1211 LAMICTAL or lamotrigine can be confused with the names of other commonly used

1212 medications. Medication errors may also occur between the different formulations of  
1213 LAMICTAL. To reduce the potential of medication errors, write and say LAMICTAL XR  
1214 clearly. Depictions of the LAMICTAL XR Extended-Release Tablets can be found in the  
1215 Medication Guide. Each LAMICTAL XR tablet has a distinct color and white center, and is  
1216 printed with “LAMICTAL XR” and the tablet strength. These distinctive features serve to  
1217 identify the different presentations of the drug and thus may help reduce the risk of medication  
1218 errors. LAMICTAL XR is supplied in round, unit-of-use bottles with orange caps containing 30  
1219 tablets. The label on the bottle includes a depiction of the tablets which further communicates to  
1220 patients and pharmacists that the medication is LAMICTAL XR and the specific tablet strength  
1221 included in the bottle. The unit-of-use bottle with a distinctive orange cap and distinctive bottle  
1222 label features serves to identify the different presentations of the drug and thus may help to  
1223 reduce the risk of medication errors. **To avoid a medication error of using the wrong drug or  
1224 formulation, patients should be strongly advised to visually inspect their tablets to verify  
1225 that they are LAMICTAL XR each time they fill their prescription and to immediately talk  
1226 to their doctor/pharmacist if they receive a LAMICTAL XR tablet without a white center  
1227 and without “LAMICTAL XR” and the strength printed on the tablet as they may have  
1228 received the wrong medication [see Dosage Forms and Strengths (3), How Supplied/Storage  
1229 and Handling (16)].**

1230  
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1233



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1236 Research Triangle Park, NC 27709

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1240 Month 2010  
1241 LXR:xPI