

NDA 022115 - FDA Approved Labeling Text dated 5/29/09

## 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)

### INDICATIONS AND USAGE

LAMICTAL XR is an antiepileptic drug (AED) indicated as adjunctive therapy for 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, 5.7)
- LAMICTAL XR should be discontinued over a period of at least 2 weeks (approximately 50% reduction per week). (2.1, 5.8)

### DOSAGE FORMS AND STRENGTHS

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

### CONTRAINDICATIONS

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

## WARNINGS AND PRECAUTIONS

- Life-threatening serious rash, and/or rash-related death, 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)
- 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, 5.6, 16, 17.9)

## ADVERSE REACTIONS

- Most common adverse reactions (treatment difference  $\geq 4\%$ , LAMICTAL XR - Placebo) are dizziness, tremor/intention tremor, cerebellar coordination/balance disorder, nausea, asthenic conditions (asthenia, fatigue, malaise), vertigo/positional vertigo, 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](http://www.fda.gov/medwatch).

## DRUG INTERACTIONS

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

## USE IN SPECIFIC POPULATIONS

- 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)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: May 2009  
LRX:1PI

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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**  
13 **rash-related death have been reported in adult and pediatric patients, but their numbers**  
14 **are too 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)*].**

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38 **1 INDICATIONS AND USAGE**

39 LAMICTAL XR is indicated as adjunctive therapy for partial onset seizures with or  
40 without secondary generalization in patients  $\geq 13$  years of age.

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

43 **2 DOSAGE AND ADMINISTRATION**

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

46 **2.1 General Dosing Considerations**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

157 **2.2 Partial Onset Seizures**

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

161

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

	For Patients TAKING Valproate*	For Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone <sup>†</sup> , or Valproate*	For Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone <sup>†</sup> and NOT TAKING Valproate*
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>‡</sup>	300 to 400 mg every day <sup>‡</sup>	400 to 600 mg every day <sup>‡</sup>

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

165 <sup>†</sup> These drugs induce glucuronidation and increase clearance [see *Drug Interactions (7),*  
166 *Clinical Pharmacology (12.3)*]. Other drugs which have similar effects include estrogen-  
167 containing oral contraceptives [see *Drug Interactions (7), Clinical Pharmacology (12.3)*].  
168 Dosing recommendations for oral contraceptives can be found in General Dosing  
169 Considerations [see *Dosage and Administration (2.1)*]. Patients on rifampin, or other drugs  
170 that induce glucuronidation and increase clearance, should follow the same dosing  
171 titration/maintenance regimen as that used with anticonvulsants that have this effect.

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

173

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

175 Patients may be converted directly from immediate-release lamotrigine to  
176 LAMICTAL XR Extended-Release Tablets. The initial dose of LAMICTAL XR should match  
177 the total daily dose of immediate-release lamotrigine. However, some subjects on concomitant

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178 enzyme-inducing agents may have lower plasma levels of lamotrigine on conversion and should  
179 be monitored [*see Clinical Pharmacology (12.3)*].

180 Following conversion to LAMICTAL XR, all patients (but especially those on an  
181 enzyme-inducing AED) should be closely monitored for seizure control. Depending on the  
182 therapeutic response after conversion, the total daily dose may need to be adjusted within the  
183 recommended dosing instructions (Table 1).

### 184 **3 DOSAGE FORMS AND STRENGTHS**

#### 185 **3.1 Extended-Release Tablets**

186 25 mg, yellow with white center, round, biconvex, film-coated tablets printed with  
187 “LAMICTAL” and “XR 25.”

188 50 mg, green with white center, round, biconvex, film-coated tablets printed with  
189 “LAMICTAL” and “XR 50.”

190 100 mg, orange with white center, round, biconvex, film-coated tablets printed with  
191 “LAMICTAL” and “XR 100.”

192 200 mg, blue with white center, round, biconvex, film-coated tablets printed with  
193 “LAMICTAL” and “XR 200.”

#### 194 **3.2 Potential Medication Errors**

195 Patients should be strongly advised to visually inspect their tablets to verify that they are  
196 receiving LAMICTAL XR, as opposed to other medications, and that they are receiving the  
197 correct formulation of LAMICTAL each time they fill their prescription. Depictions of the  
198 LAMICTAL XR tablets can be found in the Medication Guide [*see Patient Counseling*  
199 *Information (17.10)*].

### 200 **4 CONTRAINDICATIONS**

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

### 203 **5 WARNINGS AND PRECAUTIONS**

#### 204 **5.1 Serious Skin Rashes [*see Boxed Warning*]**

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

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

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216 related death in this 1,983-patient cohort. Additionally, there have been rare cases of toxic  
217 epidermal necrolysis with and without permanent sequelae and/or death in US and foreign  
218 postmarketing experience.

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

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

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

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

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

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

## 242 **5.2 Hypersensitivity Reactions**

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

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

## 254 **5.3 Acute Multiorgan Failure**

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255 Multiorgan failure, which in some cases has been fatal or irreversible, has been observed  
256 in patients receiving the immediate-release formulation of LAMICTAL. Fatalities associated  
257 with multiorgan failure and various degrees of hepatic failure have been reported in 2 of 3,796  
258 adult patients and 4 of 2,435 pediatric patients who received the immediate-release formulation  
259 of LAMICTAL in epilepsy clinical trials. Rare fatalities from multiorgan failure have been  
260 reported in compassionate plea and postmarketing use. The majority of these deaths occurred in  
261 association with other serious medical events, including status epilepticus and overwhelming  
262 sepsis, and hantavirus, making it difficult to identify the initial cause.

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

#### 271 **5.4 Blood Dyscrasias**

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

#### 276 **5.5 Suicidal Behavior and Ideation**

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

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

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

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

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

300

301 **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

302

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

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

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

## 317 **5.6 Potential Medication Errors**

318 Medication errors involving LAMICTAL have occurred. In particular, the names  
319 LAMICTAL or lamotrigine can be confused with the names of other commonly used  
320 medications. Medication errors may also occur between the different formulations of  
321 LAMICTAL. To reduce the potential of medication errors, write and say LAMICTAL XR  
322 clearly. Depictions of the LAMICTAL XR Extended-Release Tablets can be found in the  
323 Medication Guide [see Patient Counseling Information (17.10)]. Each LAMICTAL XR tablet  
324 has a distinct color and white center, and is printed with “LAMICTAL XR” and the tablet  
325 strength. These distinctive features serve to identify the different presentations of the drug and

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326 thus may help reduce the risk of medication errors. LAMICTAL XR is supplied in round, unit-  
327 of-use bottles with orange caps containing 30 tablets. The label on the bottle includes a depiction  
328 of the tablets which further communicates to patients and pharmacists that the medication is  
329 LAMICTAL XR and the specific tablet strength included in the bottle. The unit-of-use bottle  
330 with a distinctive orange cap and distinctive bottle label features serves to identify the different  
331 presentations of the drug and thus may help to reduce the risk of medication errors. To avoid the  
332 medication error of using the wrong drug or formulation, patients should be strongly advised to  
333 visually inspect their tablets to verify that they are LAMICTAL XR each time they fill their  
334 prescription.

### 335 **5.7 Concomitant Use With Oral Contraceptives**

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

### 343 **5.8 Withdrawal Seizures**

344 As with other AEDs, LAMICTAL XR should not be abruptly discontinued. In patients  
345 with epilepsy there is a possibility of increasing seizure frequency. Unless safety concerns  
346 require a more rapid withdrawal, the dose of LAMICTAL XR should be tapered over a period of  
347 at least 2 weeks (approximately 50% reduction per week) [*see Dosage and Administration*  
348 *(2.1)*].

### 349 **5.9 Status Epilepticus**

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

### 356 **5.10 Sudden Unexplained Death in Epilepsy (SUDEP)**

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

360 Some of these could represent seizure-related deaths in which the seizure was not  
361 observed, e.g., at night. This represents an incidence of 0.0035 deaths per patient-year. Although  
362 this rate exceeds that expected in a healthy population matched for age and sex, it is within the  
363 range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not  
364 receiving lamotrigine (ranging from 0.0005 for the general population of patients with epilepsy,  
365 to 0.004 for a recently studied clinical trial population similar to that in the clinical development

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366 program for immediate-release lamotrigine, to 0.005 for patients with refractory epilepsy).  
367 Consequently, whether these figures are reassuring or suggest concern depends on the  
368 comparability of the populations reported upon to the cohort receiving immediate-release  
369 lamotrigine and the accuracy of the estimates provided. Probably most reassuring is the  
370 similarity of estimated SUDEP rates in patients receiving immediate-release lamotrigine and  
371 those receiving other AEDs, chemically unrelated to each other, that underwent clinical testing in  
372 similar populations. Importantly, that drug is chemically unrelated to lamotrigine. This evidence  
373 suggests, although it certainly does not prove, that the high SUDEP rates reflect population rates,  
374 not a drug effect.

#### 375 **5.11 Addition of LAMICTAL XR to a Multidrug Regimen That Includes Valproate**

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

#### 378 **5.12 Binding in the Eye and Other Melanin-Containing Tissues**

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

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

#### 388 **5.13 Laboratory Tests**

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

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

### 399 **6 ADVERSE REACTIONS**

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

- 402 • Serious skin rashes [see *Warnings and Precautions (5.1)*]
- 403 • Hypersensitivity reactions [see *Warnings and Precautions (5.2)*]
- 404 • Acute multiorgan failure [see *Warnings and Precautions (5.3)*]

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- 405 • Blood dyscrasias [see Warnings and Precautions (5.4)]
- 406 • Suicidal behavior and ideation [see Warnings and Precautions (5.5)]
- 407 • Withdrawal seizures [see Warnings and Precautions (5.8)]
- 408 • Status epilepticus [see Warnings and Precautions (5.9)]
- 409 • Sudden unexplained death in epilepsy [see Warnings and Precautions (5.10)]

410 **6.1 Clinical Trial Experience with LAMICTAL XR for Treatment of Partial Onset**  
411 **Seizures**

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

415 The most commonly observed adverse reactions ( $\geq 4\%$  for LAMICTAL XR and more  
416 common on drug than placebo) in a double-blind, placebo-controlled trial of adjunctive therapy  
417 with LAMICTAL XR for the treatment of partial onset seizures were, in order of decreasing  
418 treatment difference (LAMICTAL XR % - Placebo %) incidence: dizziness, tremor/intention  
419 tremor, cerebellar coordination/balance disorder, nausea, asthenic conditions (asthenia, fatigue,  
420 malaise), vertigo/positional vertigo, and diplopia.

421 Nine of 118 patients (8%) treated with LAMICTAL XR who participated in the double-  
422 blind, placebo-controlled trial in the treatment of partial onset seizures discontinued treatment  
423 due to adverse reactions compared to 2 of 121 patients (2%) who received placebo. Dizziness,  
424 nausea, and nystagmus were the most common adverse reactions (based upon treatment  
425 difference of  $\geq 2\%$ ) that led to the withdrawal of subjects in the group treated with  
426 LAMICTAL XR.

427 Table 3 displays the incidence of adverse reactions in a 19-week, double-blind, placebo-  
428 controlled study of patients with partial onset seizures.

429  
430 **Table 3. Treatment-Emergent Adverse Reaction Incidence in a Double-Blind, Placebo-**  
431 **Controlled Adjunctive Trial of Patients With Partial Onset Seizures (Adverse Reactions**  
432  **$\geq 2\%$  of Patients Treated With LAMICTAL XR and More Common on Drug Than**  
433 **Placebo)**

Body System/Adverse Reaction	LAMICTAL XR (n = 118) %	Placebo (n = 121) %
Ear and Labyrinth Disorders		
Vertigo/positional vertigo	4	0
Eye Disorders		
Vision blurred	4	2
Diplopia	4	0
Gastrointestinal Disorders		
Diarrhea	8	5
Nausea	7	2

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Abdominal pain/discomfort	6	4
Vomiting	4	2
Constipation	3	1
Dry mouth	3	2
<b>General Disorders and Administration Site Conditions</b>		
Asthenic conditions (asthenia, fatigue, malaise)	9	5
Chest pain/discomfort	3	1
Gait disturbance	2	0
Pain	2	1
<b>Infections and Infestations</b>		
Influenza/influenza-like illness	3	2
Sinusitis	3	1
<b>Metabolic and Nutrition Disorders</b>		
Anorexia/decreased appetite	3	2
Weight increased	2	1
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Myalgia	3	0
<b>Nervous System</b>		
Dizziness	19	5
Somnolence	7	5
Tremor/Intention tremor	7	2
Cerebellar coordination/balance disorder	5	0
Nystagmus	3	1
<b>Psychiatric Disorders</b>		
Depression	4	1
Anxiety	3	0
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>		
Pharyngolaryngeal pain	3	2
Epistaxis	2	1
Sinus congestion	2	0
<b>Skin and Subcutaneous Tissue Disorders</b>		
Rash*	2	1
Alopecia	2	1
<b>Vascular Disorder</b>		
Hot flush	3	0

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434 \* All types of rash. In clinical trials evaluating the immediate-release formulation of  
435 LAMICTAL, the rate of serious rash was 0.3% in adults on adjunctive therapy for epilepsy  
436 [see *Boxed Warning*].  
437

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

441 The incidence for many adverse reactions caused by LAMICTAL XR treatment was  
442 increased relative to placebo (i.e., LAMICTAL XR % - Placebo % = treatment difference  $\geq 3\%$ )  
443 in either the titration or maintenance phases of the study. During the titration phase, an increased  
444 incidence (shown in descending order of % treatment difference) was observed for diarrhea,  
445 nausea, vertigo/positional vertigo, somnolence, myalgia, and hot flush. During the maintenance  
446 phase, an increased incidence was observed for dizziness, tremor/intention tremor, cerebellar  
447 coordination/balance disorder, vomiting, and diplopia. Some adverse reactions developing in the  
448 titration phase were notable for persisting ( $>7$  days) into the maintenance phase. These  
449 “persistent” adverse reactions included somnolence, dizziness, and headache. In addition, some  
450 adverse reactions had an increased likelihood of recurring. Headache recurred predominantly in  
451 the titration period and vertigo and nausea recurred throughout the whole treatment period.

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

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

## 462 **6.2 Other Adverse Reactions Observed During the Clinical Development of the** 463 **Immediate-Release Formulation of LAMICTAL**

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

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

473 *Body as a Whole:* Fever, neck pain.

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474 *Musculoskeletal*: Arthralgia.

475 *Nervous*: Insomnia, convulsion, irritability, speech disorder, concentration  
476 disturbance.

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

478 *Skin and Appendages*: Pruritus.

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

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

489 Adverse reactions are further classified within body system categories and enumerated in  
490 order of decreasing frequency using the following definitions: *frequent* adverse reactions are  
491 defined as those occurring in at least 1/100 patients; *infrequent* adverse reactions are those  
492 occurring in 1/100 to 1/1,000 patients; *rare* adverse reactions are those occurring in fewer than  
493 1/1,000 patients.

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

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

497 **Dermatological**: *Infrequent*: Acne, hirsutism, maculopapular rash, skin discoloration,  
498 and urticaria. *Rare*: Angioedema, erythema, exfoliative dermatitis, fungal dermatitis, herpes  
499 zoster, leukoderma, multiforme erythema, petechial rash, pustular rash, Stevens-Johnson  
500 syndrome, and vesiculobullous rash.

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

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

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

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

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

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

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

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

527 Urogenital System: *Infrequent*: Abnormal ejaculation, hematuria, impotence,  
528 menorrhagia, polyuria, urinary incontinence. *Rare*: Acute kidney failure, anorgasmia, breast  
529 abscess, breast neoplasm, creatinine increase, cystitis, dysuria, epididymitis, female lactation,  
530 kidney failure, kidney pain, nocturia, urinary retention, urinary urgency.

### 531 **6.3 Postmarketing Experience with the Immediate-Release Formulation of** 532 **LAMICTAL**

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

538 Blood and Lymphatic: Agranulocytosis, hemolytic anemia.

539 Gastrointestinal: Esophagitis.

540 Hepatobiliary Tract and Pancreas: Pancreatitis.

541 Immunologic: Lupus-like reaction, vasculitis.

542 Lower Respiratory: Apnea.

543 Musculoskeletal: Rhabdomyolysis has been observed in patients experiencing  
544 hypersensitivity reactions.

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

547 Non-site Specific: Progressive immunosuppression.

## 548 **7 DRUG INTERACTIONS**

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

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553

554

**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.

555 ↓ = Decreased (induces lamotrigine glucuronidation).

556 ↑ = Increased (inhibits lamotrigine glucuronidation).

557 ? = Conflicting data.

558 **8 USE IN SPECIFIC POPULATIONS**

559 **8.1 Pregnancy**

560 Teratogenic Effects: Pregnancy Category C. No evidence of teratogenicity was found in  
561 mice, rats, or rabbits when lamotrigine was orally administered to pregnant animals during the  
562 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

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563 highest usual human maintenance dose (i.e., 500 mg/day). However, maternal toxicity and  
564 secondary fetal toxicity producing reduced fetal weight and/or delayed ossification were seen in  
565 mice and rats, but not in rabbits at these doses. Teratology studies were also conducted using  
566 bolus intravenous administration of the isethionate salt of lamotrigine in rats and rabbits. In rat  
567 dams administered an intravenous dose at 0.6 times the highest usual human maintenance dose,  
568 the incidence of intrauterine death without signs of teratogenicity was increased.

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

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

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

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

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

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

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

## 607 **8.2 Labor and Delivery**

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

## 609 **8.3 Nursing Mothers**

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

## 613 **8.4 Pediatric Use**

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

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

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

## 628 **8.5 Geriatric Use**

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

## 635 **8.6 Patients With Hepatic Impairment**

636 Experience in patients with hepatic impairment is limited. Based on a clinical  
637 pharmacology study with the immediate-release formulation of LAMICTAL in 24 patients with  
638 mild, moderate, and severe liver impairment [*see Clinical Pharmacology (12.4)*], the following  
639 general recommendations can be made. No dosage adjustment is needed in patients with mild  
640 liver impairment. Initial, escalation, and maintenance doses should generally be reduced by  
641 approximately 25% in patients with moderate and severe liver impairment without ascites and

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642 50% in patients with severe liver impairment with ascites. Escalation and maintenance doses  
643 may be adjusted according to clinical response [*see Dosage and Administration (2.1)*].

## 644 **8.7 Patients With Renal Impairment**

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

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

## 655 **10 OVERDOSAGE**

### 656 **10.1 Human Overdose Experience**

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

### 661 **10.2 Management of Overdose**

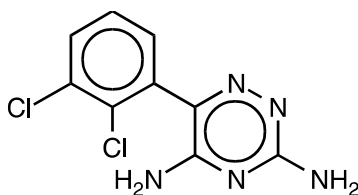
662 There are no specific antidotes for lamotrigine. Following a suspected overdose,  
663 hospitalization of the patient is advised. General supportive care is indicated, including frequent  
664 monitoring of vital signs and close observation of the patient. If indicated, emesis should be  
665 induced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

## 670 **11 DESCRIPTION**

671 LAMICTAL XR (lamotrigine), an AED of the phenyltriazine class, is chemically  
672 unrelated to existing AEDs. Its chemical name is 3,5-diamino-6-(2,3-dichlorophenyl)-*as*-triazine,  
673 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  
674 pale cream-colored powder and has a pK<sub>a</sub> of 5.7. Lamotrigine is very slightly soluble in water  
675 (0.17 mg/mL at 25°C) and slightly soluble in 0.1 M HCl (4.1 mg/mL at 25°C). The structural  
676 formula is:

677

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678  
679

680 LAMICTAL XR Extended-Release Tablets are supplied for oral administration as 25-mg  
681 (yellow with white center), 50-mg (green with white center), 100-mg (orange with white center),  
682 and 200-mg (blue with white center) tablets. Each tablet contains the labeled amount of  
683 lamotrigine and the following inactive ingredients: glycerol monostearate, hypromellose, lactose  
684 monohydrate; magnesium stearate; methacrylic acid copolymer dispersion, polyethylene glycol  
685 400, polysorbate 80, silicon dioxide (25-mg and 50-mg tablets only), titanium dioxide, triethyl  
686 citrate, iron oxide black (50-mg tablet only), iron oxide yellow (25-mg, 50-mg, 100-mg tablets  
687 only), iron oxide red (100-mg tablet only), FD&C Blue No. 2 Aluminum Lake (200-mg tablet  
688 only). Tablets are printed with edible black ink.

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

## 695 **12 CLINICAL PHARMACOLOGY**

### 696 **12.1 Mechanism of Action**

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

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

709 Although the relevance for human use is unknown, the following data characterize the  
710 performance of lamotrigine in receptor binding assays. Lamotrigine had a weak inhibitory effect  
711 on the serotonin 5-HT<sub>3</sub> receptor (IC<sub>50</sub> = 18 μM). It does not exhibit high affinity binding  
712 (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>,  
713 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

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714 opioid; muscarinic acetylcholine; and serotonin 5-HT<sub>2</sub>. Studies have failed to detect an effect of  
715 lamotrigine on dihydropyridine-sensitive calcium channels. It had weak effects at sigma opioid  
716 receptors (IC<sub>50</sub> = 145 μM). Lamotrigine did not inhibit the uptake of norepinephrine, dopamine,  
717 or serotonin, (IC<sub>50</sub>>200 μM) when tested in rat synaptosomes and/or human platelets in vitro.

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

719 Lamotrigine did not inhibit N-methyl d-aspartate (NMDA)-induced depolarizations in rat cortical  
720 slices or NMDA-induced cyclic GMP formation in immature rat cerebellum, nor did lamotrigine  
721 displace compounds that are either competitive or noncompetitive ligands at this glutamate  
722 receptor complex (CNQX, CGS, TCHP). The IC<sub>50</sub> for lamotrigine effects on NMDA-induced  
723 currents (in the presence of 3 μM of glycine) in cultured hippocampal neurons exceeded  
724 100 μM.

725 **12.2 Pharmacodynamics**

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

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

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

740 **Cardiovascular:** In dogs, lamotrigine is extensively metabolized to a 2-N-methyl  
741 metabolite. This metabolite causes dose-dependent prolongations of the PR interval, widening of  
742 the QRS complex, and, at higher doses, complete AV conduction block. Similar cardiovascular  
743 effects are not anticipated in humans because only trace amounts of the 2-N-methyl metabolite  
744 (<0.6% of lamotrigine dose) have been found in human urine [*see Clinical Pharmacology*  
745 (*12.3*)]. However, it is conceivable that plasma concentrations of this metabolite could be  
746 increased in patients with a reduced capacity to glucuronidate lamotrigine (e.g., in patients with  
747 liver disease).

748 **12.3 Pharmacokinetics**

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

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

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

764 The steady-state trough concentrations for extended-release lamotrigine were similar to  
765 or higher than those of immediate-release lamotrigine depending on concomitant AED (Table 5).  
766 A mean reduction in the lamotrigine  $C_{max}$  by 11% to 29% was observed for LAMICTAL XR  
767 compared to immediate-release lamotrigine resulting in a decrease in the peak-to-trough  
768 fluctuation in serum lamotrigine concentrations. However, in some subjects receiving enzyme-  
769 inducing AEDs, a reduction in  $C_{max}$  of 44% to 77% was observed. The degree of fluctuation was  
770 reduced by 17% in patients taking enzyme-inducing AEDs, 34% in patients taking VPA, and  
771 37% in patients taking AEDs other than carbamazepine, phenytoin, phenobarbital, primidone, or  
772 VPA. LAMICTAL XR and immediate-release lamotrigine regimens were similar with respect to  
773 area under the curve (AUC, a measure of the extent of bioavailability) for patients receiving  
774 AEDs other than those known to induce the metabolism of lamotrigine. The relative  
775 bioavailability of extended-release lamotrigine was approximately 21% lower than immediate-  
776 release lamotrigine in subjects receiving enzyme-inducing AEDs. However, in some subjects in  
777 this group a reduction in exposure of up to 70% was observed when switched to  
778 LAMICTAL XR. Therefore, doses may need to be adjusted in some subjects based on  
779 therapeutic response.

780

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

Concomitant AED	AUC <sub>(0-24ss)</sub>	$C_{max}$	$C_{min}$
EIAEDs*	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* or VPA	1.00 (0.88, 1.14)	0.89 (0.78, 1.03)	1.14 (1.03, 1.25)

783 \* EIAEDs include carbamazepine, phenytoin, phenobarbital, and primidone.

784

785 Dose Proportionality: In healthy volunteers not receiving any other medications and  
786 given LAMICTAL XR once daily, the systemic exposure to lamotrigine increased in direct  
787 proportion to the dose administered over the range of 50 to 200 mg. At doses between 25 and

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788 50 mg, the increase was less than dose proportional, with a 2-fold increase in dose resulting in an  
789 approximately 1.6-fold increase in systemic exposure.

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

794 Protein Binding: Data from in vitro studies indicate that lamotrigine is approximately  
795 55% bound to human plasma proteins at plasma lamotrigine concentrations from 1 to 10 mcg/mL  
796 (10 mcg/mL is 4 to 6 times the trough plasma concentration observed in the controlled efficacy  
797 trials). Because lamotrigine is not highly bound to plasma proteins, clinically significant  
798 interactions with other drugs through competition for protein binding sites are unlikely. The  
799 binding of lamotrigine to plasma proteins did not change in the presence of therapeutic  
800 concentrations of phenytoin, phenobarbital, or valproate. Lamotrigine did not displace other  
801 AEDs (carbamazepine, phenytoin, phenobarbital) from protein binding sites.

802 Metabolism: Lamotrigine is metabolized predominantly by glucuronic acid conjugation;  
803 the major metabolite is an inactive 2-N-glucuronide conjugate. After oral administration of  
804 240 mg of <sup>14</sup>C-lamotrigine (15 µCi) to 6 healthy volunteers, 94% was recovered in the urine and  
805 2% was recovered in the feces. The radioactivity in the urine consisted of unchanged lamotrigine  
806 (10%), the 2-N-glucuronide (76%), a 5-N-glucuronide (10%), a 2-N-methyl metabolite (0.14%),  
807 and other unidentified minor metabolites (4%).

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

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

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

821 Since the half-life of lamotrigine following administration of single doses of immediate-  
822 release lamotrigine is comparable to that observed following administration of LAMICTAL XR,  
823 similar changes in the half-life of lamotrigine would be expected for LAMICTAL XR.  
824

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825 **Table 6. Mean\* Pharmacokinetic Parameters of Immediate-release**  
826 **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>†</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>†</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)

827 \* The majority of parameter means determined in each study had coefficients of variation  
828 between 20% and 40% for half-life and Cl/F and between 30% and 70% for T<sub>max</sub>. The overall

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829 mean values were calculated from individual study means that were weighted based on the  
830 number of volunteers/patients in each study. The numbers in parentheses below each  
831 parameter mean represent the range of individual volunteer/patient values across studies.  
832 † Carbamazepine, phenobarbital, phenytoin, and primidone have been shown to increase the  
833 apparent clearance of lamotrigine. Estrogen-containing oral contraceptives and other drugs  
834 that induce lamotrigine glucuronidation have also been shown to increase the apparent  
835 clearance of lamotrigine [see *Drug Interactions (7)*].

836  
837 **Drug Interactions:** The apparent clearance of lamotrigine is affected by the  
838 coadministration of certain medications [see *Warnings and Precautions (5.7, 5.11), Drug*  
839 *Interactions (7)*].

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

843

844 **Table 7. Summary of Drug Interactions With Lamotrigine**

Drug	Drug Plasma Concentration With Adjunctive Lamotrigine*	Lamotrigine Plasma Concentration With Adjunctive Drugs†
Oral contraceptives (e.g., ethinylestradiol/levonorgestrel‡	↔§	↓
Bupropion	Not assessed	↔
Carbamazepine (CBZ)	↔	↓
CBZ epoxide	?	
Felbamate	Not assessed	↔
Gabapentin	Not assessed	↔
Levetiracetam	↔	↔
Lithium	↔	Not assessed
Olanzapine	↔	↔¶
Oxcarbazepine	↔	↔
10-monohydroxy oxcarbazepine metabolite#	↔	
Phenobarbital/primidone	↔	↓
Phenytoin (PHT)	↔	↓
Pregabalin	↔	↔
Rifampin	Not assessed	↓
Topiramate	↔**	↔
Valproate	↓	↑
Valproate + PHT and/or CBZ	Not assessed	↔

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Zonisamide	Not assessed	↔
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845 \* From adjunctive clinical trials and volunteer studies.

846 † Net effects were estimated by comparing the mean clearance values obtained in adjunctive  
847 clinical trials and volunteer studies.

848 ‡ The effect of other hormonal contraceptive preparations or hormone replacement therapy on  
849 the pharmacokinetics of lamotrigine has not been systematically evaluated in clinical trials,  
850 although the effect may be similar to that seen with the ethinylestradiol/levonorgestrel  
851 combinations.

852 § Modest decrease in levonorgestrel.

853 || Not administered, but an active metabolite of carbamazepine.

854 ¶ Slight decrease, not expected to be clinically relevant.

855 # Not administered, but an active metabolite of oxcarbazepine.

856 \*\* Slight increase not expected to be clinically relevant.

857 ↔ = No significant effect.

858 ? = Conflicting data.

859

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

867 Gradual transient increases in lamotrigine plasma levels (approximate 2-fold increase)  
868 occurred during the week of inactive hormone preparation (“pill-free” week) for women not also  
869 taking a drug that increased the clearance of lamotrigine (carbamazepine, phenytoin,  
870 phenobarbital, primidone, or other drugs that induce lamotrigine glucuronidation [*see Drug*  
871 *Interactions (7)*]). The increase in lamotrigine plasma levels will be greater if the dose of  
872 LAMICTAL XR is increased in the few days before or during the “pill-free” week. Increases in  
873 lamotrigine plasma levels could result in dose-dependent adverse effects.

874 In the same study, coadministration of lamotrigine (300 mg/day) in 16 female volunteers  
875 did not affect the pharmacokinetics of the ethinylestradiol component of the oral contraceptive  
876 preparation. There were mean decreases in the AUC and  $C_{max}$  of the levonorgestrel component of  
877 19% and 12%, respectively. Measurement of serum progesterone indicated that there was no  
878 hormonal evidence of ovulation in any of the 16 volunteers, although measurement of serum  
879 FSH, LH, and estradiol indicated that there was some loss of suppression of the hypothalamic-  
880 pituitary-ovarian axis.

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

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

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

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

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

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

907 The addition of carbamazepine decreases lamotrigine steady-state concentrations by  
908 approximately 40%.

909 Esomeprazole: In a study of 30 subjects, coadministration of LAMICTAL XR with  
910 esomeprazole resulted in no significant change in lamotrigine levels and a small decrease in T<sub>max</sub>.  
911 The levels of gastric pH were not altered compared with pre-lamotrigine dosing.

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

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

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

920 Levetiracetam: Potential drug interactions between levetiracetam and lamotrigine were  
921 assessed by evaluating serum concentrations of both agents during placebo-controlled clinical

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922 trials. These data indicate that lamotrigine does not influence the pharmacokinetics of  
923 levetiracetam and that levetiracetam does not influence the pharmacokinetics of lamotrigine.

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

926 Olanzapine: The AUC and C<sub>max</sub> of olanzapine were similar following the addition of  
927 olanzapine (15 mg once daily) to lamotrigine (200 mg once daily) in healthy male volunteers  
928 (n = 16) compared with the AUC and C<sub>max</sub> in healthy male volunteers receiving olanzapine alone  
929 (n = 16).

930 In the same study, the AUC and C<sub>max</sub> of lamotrigine were reduced on average by 24%  
931 and 20%, respectively, following the addition of olanzapine to lamotrigine in healthy male  
932 volunteers compared with those receiving lamotrigine alone. This reduction in lamotrigine  
933 plasma concentrations is not expected to be clinically relevant.

934 Oxcarbazepine: The AUC and C<sub>max</sub> of oxcarbazepine and its active 10-monohydroxy  
935 oxcarbazepine metabolite were not significantly different following the addition of  
936 oxcarbazepine (600 mg twice daily) to lamotrigine (200 mg once daily) in healthy male  
937 volunteers (n = 13) compared with healthy male volunteers receiving oxcarbazepine alone  
938 (n = 13).

939 In the same study, the AUC and C<sub>max</sub> of lamotrigine were similar following the addition  
940 of oxcarbazepine (600 mg twice daily) to lamotrigine in healthy male volunteers compared with  
941 those receiving lamotrigine alone. Limited clinical data suggest a higher incidence of headache,  
942 dizziness, nausea, and somnolence with coadministration of lamotrigine and oxcarbazepine  
943 compared with lamotrigine alone or oxcarbazepine alone.

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

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

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

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

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

957 Valproate: When lamotrigine was administered to healthy volunteers (n = 18) receiving  
958 valproate, the trough steady-state valproate plasma concentrations decreased by an average of  
959 25% over a 3-week period, and then stabilized. However, adding lamotrigine to the existing  
960 therapy did not cause a change in valproate plasma concentrations in either adult or pediatric  
961 patients in controlled clinical trials.

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

966 Zonisamide: In a study of 18 patients with epilepsy, coadministration of zonisamide  
967 (200 to 400 mg/day) with lamotrigine (150 to 500 mg/day for 35 days) had no significant effect  
968 on the pharmacokinetics of lamotrigine.

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

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

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

979 Special Populations: Patients With Renal Impairment: Twelve volunteers with  
980 chronic renal failure (mean creatinine clearance: 13 mL/min; range: 6 to 23) and another  
981 6 individuals undergoing hemodialysis were each given a single 100 mg dose of immediate-  
982 release lamotrigine. The mean plasma half-lives determined in the study were 42.9 hours  
983 (chronic renal failure), 13.0 hours (during hemodialysis), and 57.4 hours (between hemodialysis)  
984 compared with 26.2 hours in healthy volunteers. On average, approximately 20% (range: 5.6 to  
985 35.1) of the amount of lamotrigine present in the body was eliminated by hemodialysis during a  
986 4-hour session [see Dosage and Administration (2.1)].

987 Hepatic Disease: The pharmacokinetics of lamotrigine following a single 100-mg  
988 dose of immediate-release lamotrigine were evaluated in 24 subjects with mild, moderate, and  
989 severe hepatic impairment (Child-Pugh Classification system) and compared with 12 subjects  
990 without hepatic impairment. The patients with severe hepatic impairment were without ascites  
991 (n = 2) or with ascites (n = 5). The mean apparent clearances of lamotrigine in patients with mild  
992 (n = 12), moderate (n = 5), severe without ascites (n = 2), and severe with ascites (n = 5) liver  
993 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,  
994 as compared with  $0.37 \pm 0.1$  mL/min/kg in the healthy controls. Mean half-lives of lamotrigine  
995 in patients with mild, moderate, severe without ascites, and severe with ascites hepatic  
996 impairment were  $46 \pm 20$ ,  $72 \pm 44$ ,  $67 \pm 11$ , and  $100 \pm 48$  hours, respectively, as compared with  
997  $33 \pm 7$  hours in healthy controls [see Dosage and Administration (2.1)].

998 Elderly: The pharmacokinetics of lamotrigine following a single 150 mg dose of  
999 immediate-release lamotrigine were evaluated in 12 elderly volunteers between the ages of 65  
1000 and 76 years (mean creatinine clearance: 61 mL/min, range: 33 to 108 mL/min). The mean half-

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1001 life of lamotrigine in these subjects was 31.2 hours (range: 24.5 to 43.4 hours), and the mean  
1002 clearance was 0.40 mL/min/kg (range: 0.26 to 0.48 mL/min/kg).

1003 *Gender:* The clearance of lamotrigine is not affected by gender. However, during  
1004 dose escalation of immediate-release lamotrigine in one clinical trial in patients with epilepsy on  
1005 a stable dose of valproate (n = 77), mean trough lamotrigine concentrations, unadjusted for  
1006 weight, were 24% to 45% higher (0.3 to 1.7 mcg/mL) in females than in males.

1007 *Race:* The apparent oral clearance of lamotrigine was 25% lower in non-Caucasians  
1008 than Caucasians.

1009 *Pediatric Patients:* Safety and effectiveness of LAMICTAL XR for use in patients  
1010 below the age of 13 have not been established.

## 1011 **13 NONCLINICAL TOXICOLOGY**

### 1012 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

1013 No evidence of carcinogenicity was seen in 1 mouse study or 2 rat studies following oral  
1014 administration of lamotrigine for up to 2 years at maximum tolerated doses (30 mg/kg/day for  
1015 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>,  
1016 respectively). Steady-state plasma concentrations ranged from 1 to 4 mcg/mL in the mouse study  
1017 and 1 to 10 mcg/mL in the rat study. Plasma concentrations associated with the recommended  
1018 human doses of 300 to 500 mg/day are generally in the range of 2 to 5 mcg/mL, but  
1019 concentrations as high as 19 mcg/mL have been recorded.

1020 Lamotrigine was not mutagenic in the presence or absence of metabolic activation when  
1021 tested in 2 gene mutation assays (the Ames test and the in vitro mammalian mouse lymphoma  
1022 assay). In 2 cytogenetic assays (the in vitro human lymphocyte assay and the in vivo rat bone  
1023 marrow assay), lamotrigine did not increase the incidence of structural or numerical  
1024 chromosomal abnormalities.

1025 No evidence of impairment of fertility was detected in rats given oral doses of  
1026 lamotrigine up to 2.4 times the highest usual human maintenance dose of 8.33 mg/kg/day or  
1027 0.4 times the human dose on a mg/m<sup>2</sup> basis. The effect of lamotrigine on human fertility is  
1028 unknown.

## 1029 **14 CLINICAL STUDIES**

### 1030 **14.1 Partial Onset Seizures**

1031 The effectiveness of immediate-release lamotrigine as adjunctive therapy (added to other  
1032 AEDs) was initially established in 3 pivotal multicenter, placebo-controlled, double-blind  
1033 clinical trials in 355 adults with refractory partial onset seizures.

1034 The effectiveness of LAMICTAL XR as adjunctive therapy in partial onset seizures, with  
1035 or without secondary generalization, was established in a 19-week, multicenter, double-blind,  
1036 placebo-controlled trial in 236 patients, 13 years of age and older (approximately 93% of patients  
1037 were 16 to 65 years old). Approximately 36% were from the U.S. and approximately 64% were  
1038 from other countries including Argentina, Brazil, Chile, Germany, India, Korea, Russian  
1039 Federation, and Ukraine. Patients with at least 8 partial onset seizures during an 8-week

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1040 prospective baseline phase (or 4-week prospective baseline coupled with a 4-week historical  
1041 baseline documented with seizure diary data) were randomized to treatment with  
1042 LAMICTAL XR (n = 116) or placebo (n = 120) added to their current regimen of 1 or 2 AEDs.  
1043 Approximately half of the patients were taking 2 concomitant AEDs at baseline. Target doses  
1044 ranged from 200 to 500 mg/day of LAMICTAL XR based on concomitant AED (target dose =  
1045 200 mg for valproate, 300 mg for AEDs not altering plasma lamotrigine, and 500 mg for  
1046 enzyme-inducing AEDs). The median partial seizure frequency per week at baseline was 2.3 for  
1047 LAMICTAL XR and 2.1 for placebo.

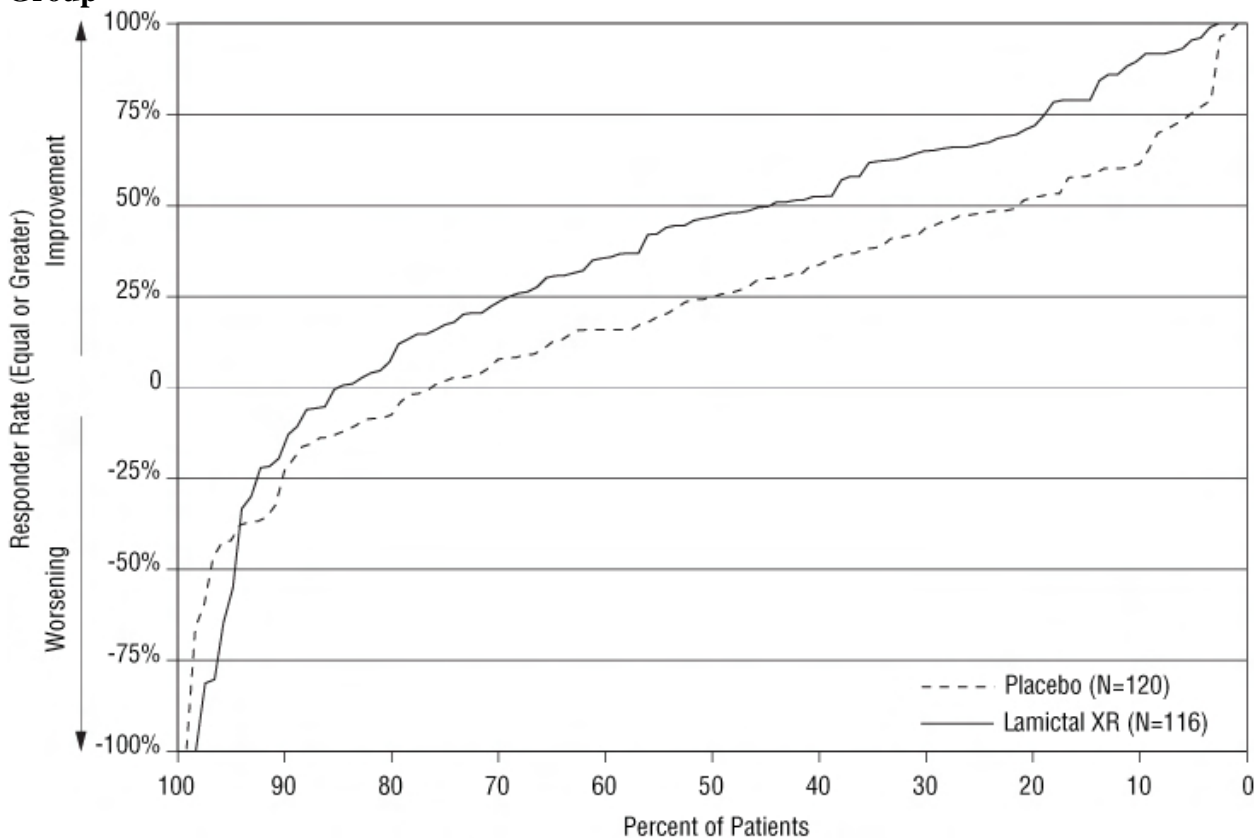
1048 The primary endpoint was the median percent change from baseline in partial onset  
1049 seizure frequency during the entire double-blind treatment phase. The median percent reductions  
1050 in weekly partial onset seizures were 47% in patients treated with LAMICTAL XR and 25% on  
1051 placebo, a difference that was statistically significant.

1052 Figure 1 presents the percentage of patients (X-axis) with a percent reduction in partial  
1053 seizure frequency (responder rate) from baseline to the entire treatment period at least as great as  
1054 that represented on the Y-axis. A positive value on the Y-axis indicates an improvement from  
1055 baseline (i.e., a decrease in seizure frequency), while a negative value indicates a worsening from  
1056 baseline (i.e., an increase in seizure frequency). Thus, in a display of this type, a curve for an  
1057 effective treatment is shifted to the left of the curve for placebo. The proportion of patients  
1058 achieving any particular level of reduction in seizure frequency was consistently higher for the  
1059 group treated with LAMICTAL XR compared with the placebo group. For example, 44% of  
1060 patients randomized to LAMICTAL XR experienced a 50% or greater reduction in seizure  
1061 frequency, compared with 21% of patients randomized to placebo. Patients with an increase in  
1062 seizure frequency >100% are represented on the Y-axis as equal to or greater than -100%.

1063

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1064 **Figure 1. Proportion of Patients by Responder Rate for LAMICTAL XR and Placebo**  
1065 **Group**



1066  
1067

1068 **16 HOW SUPPLIED/STORAGE AND HANDLING**

1069 **LAMICTAL XR (lamotrigine) Extended-Release Tablets**

1070 25 mg, yellow with a white center, round, biconvex, film-coated tablets printed on one  
1071 face in black ink with "LAMICTAL" and "XR 25", unit-of-use bottles of 30 with orange caps  
1072 (NDC 0173-0754-00).

1073 50 mg, green with a white center, round, biconvex, film-coated tablets printed on one  
1074 face in black ink with "LAMICTAL" and "XR 50", unit-of-use bottles of 30 with orange caps  
1075 (NDC 0173-0755-00).

1076 100 mg, orange with a white center, round, biconvex, film-coated tablets printed on one  
1077 face in black ink with "LAMICTAL" and "XR 100", unit-of-use bottles of 30 with orange caps  
1078 (NDC 0173-0756-00).

1079 200 mg, blue with a white center, round, biconvex, film-coated tablets printed on one  
1080 face in black ink with "LAMICTAL" and "XR 200", unit-of-use bottles of 30 with orange caps  
1081 (NDC 0173-0757-00).

1082 **LAMICTAL XR (lamotrigine) Patient Titration Kit for Patients Taking Valproate**  
1083 **(Blue XR Kit)**

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1084 25 mg, yellow with a white center, round, biconvex, film-coated tablets printed on one  
1085 face in black ink with "LAMICTAL" and "XR 25" and 50 mg, green with a white center, round,  
1086 biconvex, film-coated tablets printed on one face in black ink with "LAMICTAL" and "XR 50";  
1087 blisterpack of 21/25-mg tablets and 7/50-mg tablets (NDC 0173-0758-00).

1088 **LAMICTAL XR (lamotrigine) Patient Titration Kit for Patients Taking**  
1089 **Carbamazepine, Phenytoin, Phenobarbital, or Primidone, and Not Taking Valproate**  
1090 **(Green XR Kit)**

1091 50 mg, green with a white center, round, biconvex, film-coated tablets printed on one  
1092 face in black ink with "LAMICTAL" and "XR 50"; 100 mg, orange with a white center, round,  
1093 biconvex, film-coated tablets printed on one face in black ink with "LAMICTAL" and "XR 100";  
1094 and 200 mg, blue with a white center, round, biconvex, film-coated tablets printed on one face in  
1095 black ink with "LAMICTAL" and "XR 200"; blisterpack of 14/50-mg tablets, 14/100-mg tablets,  
1096 and 7/200-mg tablets (NDC 0173-0759-00).

1097 **LAMICTAL XR (lamotrigine) Patient Titration Kit for Patients Not Taking**  
1098 **Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate (Orange XR Kit)**

1099 25 mg, yellow with a white center, round, biconvex, film-coated tablets printed on one  
1100 face in black ink with "LAMICTAL" and "XR 25"; 50 mg, green with a white center, round,  
1101 biconvex, film-coated tablets printed on one face in black ink with "LAMICTAL" and "XR 50";  
1102 and 100 mg, orange with a white center, round, biconvex, film-coated tablets printed on one face  
1103 in black ink with "LAMICTAL" and "XR 100"; blisterpack of 14/25-mg tablets, 14/50-mg  
1104 tablets, and 7/100-mg tablets (NDC 0173-0760-00).

1105 **Storage:** Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP  
1106 Controlled Room Temperature].

1107 **17 PATIENT COUNSELING INFORMATION**

1108 See Medication Guide (17.10).

1109 **17.1 Rash**

1110 Prior to initiation of treatment with LAMICTAL XR, the patient should be instructed that  
1111 a rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy) may herald  
1112 a serious medical event and that the patient should report any such occurrence to a physician  
1113 immediately.

1114 **17.2 Suicidal Thinking and Behavior**

1115 Patients, their caregivers, and families should be counseled that AEDs, including  
1116 LAMICTAL XR, may increase the risk of suicidal thoughts and behavior and should be advised  
1117 of the need to be alert for the emergence or worsening of symptoms of depression, any unusual  
1118 changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about  
1119 self-harm. Behaviors of concern should be reported immediately to healthcare providers.

1120 **17.3 Worsening of Seizures**

1121 Patients should be advised to notify their physician if worsening of seizure control  
1122 occurs.

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1123 **17.4 CNS Adverse Effects**

1124 Patients should be advised that LAMICTAL XR may cause dizziness, somnolence, and  
1125 other symptoms and signs of central nervous system (CNS) depression. Accordingly, they should  
1126 be advised neither to drive a car nor to operate other complex machinery until they have gained  
1127 sufficient experience on LAMICTAL XR to gauge whether or not it adversely affects their  
1128 mental and/or motor performance.

1129 **17.5 Blood Dyscrasias and/or Acute Multiorgan Failure**

1130 Patients should be advised of the possibility of blood dyscrasias and/or acute multiorgan  
1131 failure and to contact their physician immediately if they experience any signs or symptoms of  
1132 these conditions [*see Warnings and Precautions (5.3, 5.4)*].

1133 **17.6 Pregnancy**

1134 Patients should be advised to notify their physicians if they become pregnant or intend to  
1135 become pregnant during therapy. Patients should be advised to notify their physicians if they  
1136 intend to breastfeed or are breastfeeding an infant.

1137 Patients should also be encouraged to enroll in the NAAED Pregnancy Registry if they  
1138 become pregnant. This registry is collecting information about the safety of antiepileptic drugs  
1139 during pregnancy. To enroll, patients can call the toll-free number 1-888-233-2334 [*see Use in*  
1140 *Specific Populations (8.1)*].

1141 **17.7 Oral Contraceptive Use**

1142 Women should be advised to notify their physician if they plan to start or stop use of oral  
1143 contraceptives or other female hormonal preparations. Starting estrogen-containing oral  
1144 contraceptives may significantly decrease lamotrigine plasma levels and stopping estrogen-  
1145 containing oral contraceptives (including the “pill-free” week) may significantly increase  
1146 lamotrigine plasma levels [*see Warnings and Precautions (5.7), Clinical Pharmacology (12.3)*].  
1147 Women should also be advised to promptly notify their physician if they experience adverse  
1148 reactions or changes in menstrual pattern (e.g., break-through bleeding) while receiving  
1149 LAMICTAL XR in combination with these medications.

1150 **17.8 Discontinuing LAMICTAL XR**

1151 Patients should be advised to notify their physician if they stop taking LAMICTAL XR  
1152 for any reason and not to resume LAMICTAL XR without consulting their physician.

1153 **17.9 Potential Medication Errors**

1154 Medication errors involving LAMICTAL have occurred. In particular the name  
1155 LAMICTAL or lamotrigine can be confused with the names of other commonly used  
1156 medications. Medication errors may also occur between the different formulations of  
1157 LAMICTAL. To reduce the potential of medication errors, write and say LAMICTAL XR  
1158 clearly. Depictions of the LAMICTAL XR Extended-Release Tablets can be found in the  
1159 Medication Guide in section 17.10. Each LAMICTAL XR tablet has a distinct color and white  
1160 center, and is printed with “LAMICTAL XR” and the tablet strength. These distinctive features  
1161 serve to identify the different presentations of the drug and thus may help reduce the risk of  
1162 medication errors. LAMICTAL XR is supplied in round, unit-of-use bottles with orange caps  
1163 containing 30 tablets. The label on the bottle includes a depiction of the tablets which further

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1164 communicates to patients and pharmacists that the medication is LAMICTAL XR and the  
1165 specific tablet strength included in the bottle. The unit-of-use bottle with a distinctive orange cap  
1166 and distinctive bottle label features serves to identify the different presentations of the drug and  
1167 thus may help to reduce the risk of medication errors. **To avoid a medication error of using the**  
1168 **wrong drug or formulation, patients should be strongly advised to visually inspect their**  
1169 **tablets to verify that they are LAMICTAL XR each time they fill their prescription and to**  
1170 **immediately talk to their doctor/pharmacist if they receive a LAMICTAL XR tablet**  
1171 **without a white center and without “LAMICTAL XR” and the strength printed on the**  
1172 **tablet as they may have received the wrong medication** [see *Dosage Forms and Strengths (3),*  
1173 *How Supplied/Storage and Handling (16)*].

#### 1174 **17.10 Medication Guide**

1175 A Medication Guide is provided as a separate leaflet accompanying the product. The full  
1176 text of the Medication Guide is reprinted below.

1177

### 1178 **MEDICATION GUIDE**

1179

#### 1180 **LAMICTAL<sup>®</sup> XR<sup>™</sup> (lamotrigine) Extended-Release Tablets**

1181

1182 Read this Medication Guide before you start taking LAMICTAL XR and each time you get a  
1183 refill. There may be new information. This information does not take the place of talking with  
1184 your healthcare provider about your medical condition or treatment. If you have questions about  
1185 LAMICTAL XR, ask your healthcare provider or pharmacist.

1186

#### 1187 **What is the most important information I should know about LAMICTAL XR?**

1188 **1. LAMICTAL XR may cause a serious skin rash that may cause you to be hospitalized or**  
1189 **to stop LAMICTAL XR; it may rarely cause death.**

1190 There is no way to tell if a mild rash will develop into a more serious reaction. These serious  
1191 skin reactions are more likely to happen when you begin taking LAMICTAL XR, within the  
1192 first 2 to 8 weeks of treatment. But it can happen in people who have taken LAMICTAL XR  
1193 for any period of time. Children between 2 to 16 years of age have a higher chance of getting  
1194 this serious skin reaction while taking lamotrigine. LAMICTAL XR is not approved for use  
1195 in children less than 13 years old.

1196 The risk of getting a rash is higher if you:

- 1197 • take LAMICTAL XR while taking valproate (DEPAKENE (valproic acid) or
- 1198 DEPAKOTE (divalproex sodium)).
- 1199 • take a higher starting dose of LAMICTAL XR than your healthcare provider prescribed.
- 1200 • increase your dose of LAMICTAL XR faster than prescribed.

1201

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1202 **LAMICTAL XR can also cause other types of allergic reactions or serious problems**  
1203 **which may affect organs and other parts of your body like the liver or blood cells. You**  
1204 **may or may not have a rash with these types of reactions.**

1205 **Call your healthcare provider right away if you have any of the following:**

- 1206 • a skin rash
- 1207 • hives
- 1208 • fever
- 1209 • swollen lymph glands
- 1210 • painful sores in the mouth or around your eyes
- 1211 • swelling of your lips or tongue
- 1212 • yellowing of your skin or eyes
- 1213 • unusual bruising or bleeding
- 1214 • severe fatigue or weakness
- 1215 • severe muscle pain
- 1216 • frequent infections

1217

1218 These symptoms may be the first signs of a serious reaction. A healthcare provider should  
1219 examine you to decide if you should continue taking LAMICTAL XR.

1220 **2. Like other antiepileptic drugs, LAMICTAL XR may cause suicidal thoughts or actions**  
1221 **in a very small number of people, about 1 in 500.**

1222 **Call a healthcare provider right away if you have any of these symptoms, especially if**  
1223 **they are new, worse, or worry you:**

- 1224 • thoughts about suicide or dying
- 1225 • attempt to commit suicide
- 1226 • new or worse depression
- 1227 • new or worse anxiety
- 1228 • feeling agitated or restless
- 1229 • panic attacks
- 1230 • trouble sleeping (insomnia)
- 1231 • new or worse irritability
- 1232 • acting aggressive, being angry, or violent
- 1233 • acting on dangerous impulses
- 1234 • an extreme increase in activity and talking (mania)
- 1235 • other unusual changes in behavior or mood

1236 **Do not stop LAMICTAL XR without first talking to a healthcare provider.**

- 1237 • Stopping LAMICTAL XR suddenly can cause serious problems.
- 1238 • Suicidal thoughts or actions can be caused by things other than medicines. If you have
- 1239 suicidal thoughts or actions, your healthcare provider may check for other causes.

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1240 **How can I watch for early symptoms of suicidal thoughts and actions?**

- 1241 • Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or  
1242 feelings.  
1243 • Keep all follow-up visits with your healthcare provider as scheduled.  
1244 • Call your healthcare provider between visits as needed, especially if you are worried  
1245 about symptoms.

1246 **LAMICTAL XR can have other serious side effects.** For more information ask your  
1247 healthcare provider or pharmacist. Tell your healthcare provider if you have any side effect  
1248 that bothers you. Be sure to read the section below entitled “What are the possible side  
1249 effects of LAMICTAL XR?”

1250 **3. Patients prescribed LAMICTAL have sometimes been given the wrong medicine**  
1251 **because many medicines have names similar to LAMICTAL, so always check that you**  
1252 **receive LAMICTAL XR.**





1253 Taking the wrong medication can cause serious health problems. When your healthcare  
1254 provider gives you a prescription for LAMICTAL XR:

- 1255 • Make sure you can read it clearly.  
1256 • Talk to your pharmacist to check that you are given the correct medicine.  
1257 • Each time you fill your prescription, check the tablets you receive against the pictures of  
1258 the tablets below.

1259  
1260 These pictures show the distinct wording, colors, and shapes of the tablets that help to identify  
1261 the right strength of LAMICTAL XR. Immediately call your pharmacist if you receive a  
1262 LAMICTAL XR tablet that does not look like one of the tablets shown below, as you may  
1263 have received the wrong medication.

1264  
1265

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

 <b>25 mg, yellow with white center Imprinted with LAMICTAL XR 25</b>	 <b>50 mg, green with white center Imprinted with LAMICTAL XR 50</b>	 <b>100 mg, orange with white center Imprinted with LAMICTAL XR 100</b>	 <b>200 mg, blue with white center Imprinted with LAMICTAL XR 200</b>
-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

1266

1267 **What is LAMICTAL XR?**

1268 LAMICTAL XR is a prescription medicine used together with other medicines to treat partial  
1269 seizures in people 13 years or older.

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1270 It is not known if LAMICTAL XR is safe or effective in children under the age of 13. Other  
1271 forms of LAMICTAL can be used in children 2 to 12 years.

1272

1273 **Who should not take LAMICTAL XR?**

1274 You should not take LAMICTAL XR if you have had an allergic reaction to lamotrigine or to  
1275 any of the inactive ingredients in LAMICTAL XR. See the end of this leaflet for a complete list  
1276 of ingredients in LAMICTAL XR.

1277

1278 **What should I tell my healthcare provider before taking LAMICTAL XR?**

1279 Before taking LAMICTAL XR, tell your healthcare provider about all of your medical  
1280 conditions, including if you:

- 1281 • have had a rash or allergic reaction to another antiseizure medicine.
- 1282 • have or have had depression, mood problems or suicidal thoughts or behavior.
- 1283 • are taking oral contraceptives (birth control pills) or other female hormonal medicines. Do  
1284 not start or stop taking birth control pills or other female hormonal medicine until you have  
1285 talked with your healthcare provider. Tell your healthcare provider if you have any changes  
1286 in your menstrual pattern such as breakthrough bleeding. Stopping these medicines may  
1287 cause side effects (such as dizziness, lack of coordination, or double vision). Starting these  
1288 medicines may lessen how well LAMICTAL XR works.
- 1289 • are pregnant or plan to become pregnant. It is not known if LAMICTAL XR will harm your  
1290 unborn baby. If you become pregnant while taking LAMICTAL XR, talk to your healthcare  
1291 provider about registering with the North American Antiepileptic Drug Pregnancy Registry.  
1292 You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to  
1293 collect information about the safety of antiepileptic drugs during pregnancy.
- 1294 • are breastfeeding. LAMICTAL XR can pass into your breast milk. You and your healthcare  
1295 provider should decide if you should take LAMICTAL XR or breastfeed. Breastfeeding  
1296 while taking LAMICTAL XR is not recommended.

1297

1298 Tell your healthcare provider about all the medicines you take or if you are planning to take a  
1299 new medicine, including prescription and non-prescription medicines, vitamins, and herbal  
1300 supplements. Using LAMICTAL XR with certain other medicines can affect each other, causing  
1301 side effects.

1302

1303 **How should I take LAMICTAL XR?**

- 1304 • Take LAMICTAL XR exactly as prescribed.
- 1305 • Your healthcare provider may change your dose. Do not change your dose without talking to  
1306 your healthcare provider.

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- 1307 • Do not stop taking LAMICTAL XR without talking to your healthcare provider. Stopping  
1308 LAMICTAL XR suddenly may cause serious problems. For example, if you have epilepsy  
1309 and you stop taking LAMICTAL XR suddenly, you may get seizures that do not stop. Talk  
1310 with your healthcare provider about how to stop LAMICTAL XR slowly.
- 1311 • If you miss a dose of LAMICTAL XR, take it as soon as you remember. If it is almost time  
1312 for your next dose, just skip the missed dose. Take the next dose at your regular time. **Do not**  
1313 **take two doses at the same time.**
- 1314 • You may not feel the full effect of LAMICTAL XR for several weeks.
- 1315 • If you have epilepsy, tell your healthcare provider if your seizures get worse or if you have  
1316 any new types of seizures.
- 1317 • LAMICTAL XR can be taken with or without food.
- 1318 • Do not chew, crush, or divide LAMICTAL XR.
- 1319 • Swallow LAMICTAL XR tablets whole.
- 1320 • If you have trouble swallowing LAMICTAL XR Tablets, tell your healthcare provider  
1321 because there may be another form of LAMICTAL you can take.
- 1322 • If you receive LAMICTAL XR in a blisterpack, examine the blisterpack before use. Do not  
1323 use if blisters are torn, broken, or missing.

1324

1325 **What should I avoid while taking LAMICTAL XR?**

- 1326 • Do not drive a car or operate complex, hazardous machinery until you know how  
1327 LAMICTAL XR affects you.

1328

1329 **What are possible side effects of LAMICTAL XR?**

- 1330 • See “What is the most important information I should know about LAMICTAL XR?”

1331 Common side effects of LAMICTAL XR include:

• dizziness	• double vision
• diarrhea	• nausea
• weakness or fatigue	• depression
• difficulty with coordination or balance	• muscle ache
• tremor	• nervousness
• hot flashes	

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1333 Other common side effects that have been reported with another form of LAMICTAL include  
1334 headache, sleepiness, and vomiting,

1335

1336 Tell your healthcare provider about any side effect that bothers you or that does not go away.

1337 These are not all the possible side effects of LAMICTAL XR. For more information, ask your  
1338 healthcare provider or pharmacist.

1339 Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-  
1340 800-FDA-1088.

1341

#### 1342 **How should I store LAMICTAL XR?**

1343 • Store LAMICTAL XR at room temperature between 59°F to 86°F (15°C to 30°C).

1344 • **Keep LAMICTAL XR and all medicines out of the reach of children.**

1345

#### 1346 **General information about LAMICTAL XR**

1347 Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.  
1348 Do not use LAMICTAL XR for a condition for which it was not prescribed. Do not give  
1349 LAMICTAL XR to other people, even if they have the same symptoms you have. It may harm  
1350 them.

1351 This Medication Guide summarizes the most important information about LAMICTAL XR. If  
1352 you would like more information, talk with your healthcare provider. You can ask your  
1353 healthcare provider or pharmacist for information about LAMICTAL XR that is written for  
1354 healthcare professionals.

1355

1356 For more information, go to [www.lamictalxr.com](http://www.lamictalxr.com) or call 1-888-825-5249.

1357

#### 1358 **What are the ingredients in LAMICTAL XR?**

1359 Active ingredient: Lamotrigine.

1360 Inactive ingredients: glycerol monostearate, hypromellose, lactose monohydrate; magnesium  
1361 stearate; methacrylic acid copolymer dispersion, polyethylene glycol 400, polysorbate 80, silicon  
1362 dioxide (25 mg and 50 mg tablets only), titanium dioxide, triethyl citrate, iron oxide black (50  
1363 mg tablet only), iron oxide yellow (25 mg, 50 mg, 100 mg tablets only), iron oxide red (100 mg  
1364 tablet only), FD&C Blue No. 2 Aluminum Lake (200 mg tablet only). Tablets are printed with  
1365 edible black ink.

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1366 **This Medication Guide has been approved by the U.S. Food and Drug Administration.**

1367

1368 May 2009

1369 LMT:1MG

1370

1371



GlaxoSmithKline

1372

1373 GlaxoSmithKline

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**NDA 022251 LAMICTAL (lamotrigine) ODT (Orally Disintegrating Tablets)**

**NDA 22-115 Lamictal (lamotrigine) XR (Extended Release Tablets)**

**NDA 20-241 Lamictal (lamotrigine) Tablets**

**NDA 20-764 Lamictal (lamotrigine) Chewable Dispersible Tablets**

**RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

**I. GOAL:**

The goal of the REMS is to inform patients of the serious risks associated with Lamictal, including the increased risk of suicidal thoughts and behavior.

**II. REMS ELEMENTS**

**A. Medication Guide**

A Medication Guide will be dispensed with each LAMICTAL prescription.

- LAMICTAL ODT, LAMICTAL XR, and certain packages of LAMICTAL Chewable Dispersible Tablets and Tablets are packaged as a single unit of use and a Medication Guide will be attached to each package. Each Medication Guide is barcode scanned to ensure that the correct version is being used and that the component is available for attaching to each package.
- LAMICTAL Chewable Dispersible Tablets and Tablets that are not unit-of-use will have sufficient numbers of Medication Guides affixed/enclosed with each package/container. Each Medication Guide is barcode scanned to ensure that the correct version is being used and that the component is available for attaching to each package.

The label of each container or package of LAMICTAL will include a prominent instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and state how the Medication Guide is provided. Please see the appended Medication Guide.

**B. Communication Plan**

Not applicable.

**C. Elements to Assure Safe Use**

Not applicable.

**D. Implementation System**

Not applicable.

### **III. Timetable for Submission of Assessments**

REMS Assessments will be submitted to FDA 18 months, 3 years, and 7 years following REMS approval. GlaxoSmithKline will submit the assessments within 60 days of the closure of the intervals.

## APPENDIX 1: Specifications and Justification for Supply of Medication Guide

The Medication Guide will be affixed to bottles and enclosed in Patient Titration Kits, Conversion Kits or Maintenance Kits, including Physician Sample Kits. In instances where the bottles are NOT unit-of-use, 2 or 3 Medication Guides will be affixed to the bottle as specified in Table 1. Unit-of-use would be greater than or equal to 30 tablets and thus, a maximum of 2 Medication Guides should be affixed to bottles of 60 Tablets in order to ensure that a Medication Guide is available to be dispensed to a patient with their prescribed medication. In those instances where there are bottles of 100 tablets, the theoretical possibility of these being used to fill 4 prescriptions exists. However, data regarding the average number of tablets that are dispensed (from *Vector One: National (VONA) from SDI: see Table 1*) confirms that in practice, the average number of tablets dispensed for each prescription for Neurology and Psychiatry is such that 2 Medication Guides per prescription will be sufficient. GSK proposes to affix 3 Medication Guides to the bottles of 100 tablets to ensure that a Medication Guide will be available for each patient.

The label of each container or package of LAMICTAL will include a prominent instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and state how the Medication Guide is provided according to the following principles:

- a. When the Medication Guide is included inside the carton/container and the entire carton/container is being dispensed to the patient, the language will read:

**Dispense the enclosed Medication Guide to each patient.**

- b. When the Medication Guide is being attached/affixed to the outside of the bottle/container, the language will read:

**Dispense the accompanying Medication Guide to each patient.**

**Table 1: Provision of Medication Guides in Presentations of LAMICTAL Products That May Not be Unit-of-Use**

Formulation	Presentation	Number Med Guides	Ave Number of Tablets Dispensed per Neurology (N) and Psychiatry (P) Rx*		
			Nov08	Dec08	Jan09
LAMICTAL Chewable Dispersible Tablets	<b>Bottles</b>				
	5 mg x 100 tablets (Trade)	3	N: 172 P: 85	N: 178 P: 87	N: 167 P: 81
	25 mg x 100 tablets (Trade)	3	N: 218 P: 89	N: 214 P: 117	N: 217 P: 103
LAMICTAL Tablets	<b>Bottles</b>				
	25 mg x 100 tablets (Trade)	3	N: 119 P: 70	N: 120 P: 71	N: 124 P: 69
	100 mg x 100	3	N: 88 P: 50	N: 90 P: 50	N: 91 P: 50

	tablets (Trade)				
	150 mg x 60 tablets (Trade)	2			
	200 mg x 60 tablets (Trade)	2			
<b>LAMICTAL ODT</b>	<b>Institutional Unit Dose Packs (Blisterpacks)</b>				
	25 mg x 28 tablets	0†			
	50 mg x 28 tablets	0†			
	100 mg x 28 tablets	0†			
	200 mg x 28 tablets	0†			
<b>LAMICTAL XR Tablets</b>	<b>All Presentations are Unit-of-Use</b>				

\* Source: **Vector One: National (VONA)** from SDI; March 2007 – February 2009. This data is based on total U.S. prescriptions for LAMICTAL from March 2007 to February 2009. Data includes the average prescription size for LAMICTAL identified by strength and segmented by prescribing physician.

†Inpatient Use Only (exempt)

## **APPENDIX 2: REMS Assessments**

REMS Assessments will be submitted to FDA 18 months, 3 years, and 7 years following REMS approval. GlaxoSmithKline (GSK) will submit the assessments within 60 days of the closure of the intervals.

The following assessments are planned:

- a. A survey of the of patients' understanding of the serious risks of LAMICTAL
- b. For those presentations of LAMICTAL that are not unit-of-use, a survey of patients to determine if they are receiving the Medication Guide
  - If the survey indicates that a significant proportion of patients are not receiving the Medication Guide:
    - an assessment of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24 and a report on failures to adhere to distribution and dispensing requirements and corrective actions taken to address noncompliance will be completed.

GSK will submit the REMS Supporting Document with our methodology for these surveys at least 2 to 3 months in advance of the planned assessments.