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### HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

#### WARNING: SERIOUS SKIN RASHES

See full prescribing information for complete boxed warning.

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

- coadministration with valproate
  - exceeding recommended initial dose of LAMICTAL XR
  - exceeding recommended dose escalation for LAMICTAL XR.
- Benign rashes are also caused by lamotrigine; however, it is not possible to predict which rashes will prove to be serious or life threatening. LAMICTAL XR should be discontinued at the first sign of rash, unless the rash is clearly not drug related. (5.1)

#### RECENT MAJOR CHANGES

Indications and Usage, Monotherapy (1.2)	April 2011
Dosage and Administration, Conversion from Adjunctive Therapy to Monotherapy (2.3)	April 2011
Warnings and Precautions, Multiorgan Hypersensitivity and Organ Failure (5.2)	August 2011

#### INDICATIONS AND USAGE

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

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

#### DOSAGE AND ADMINISTRATION

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

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- 1.3 Limitation of Use

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- 2.1 General Dosing Considerations
- 2.2 Adjunctive Therapy for Primary Generalized Tonic-Clonic and Partial Onset Seizures

#### DOSAGE FORMS AND STRENGTHS

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

#### CONTRAINDICATIONS

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

#### WARNINGS AND PRECAUTIONS

- Life-threatening serious rash and/or rash-related death: Discontinue at the first sign of rash, unless the rash is clearly not drug related. (Boxed Warning, 5.1)
- Fatal or life-threatening hypersensitivity reaction: Multiorgan hypersensitivity reactions, also known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), may be fatal or life threatening. Early signs may include rash, fever, and lymphadenopathy. These reactions may be associated with other organ involvement, such as hepatitis, hepatic failure, blood dyscrasias, or acute multiorgan failure. LAMICTAL XR should be discontinued if alternate etiology for this reaction is not found. (5.2)
- Blood dyscrasias (e.g., neutropenia, thrombocytopenia, pancytopenia): May occur, either with or without an associated hypersensitivity syndrome. Monitor for signs of anemia, unexpected infection, or bleeding. (5.3)
- Suicidal behavior and ideation: Monitor for suicidal thoughts or behaviors. (5.4)
- Aseptic meningitis: Monitor for signs of meningitis. (5.5)
- Medication errors due to product name confusion: Strongly advise patients to visually inspect tablets to verify the received drug is correct. (3.2, 5.6, 16, 17.10)

#### ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](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)
- Estrogen-containing oral contraceptives and rifampin also decrease lamotrigine concentrations by approximately 50%. (7, 12.3)

#### USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2013

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

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2 **FULL PRESCRIBING INFORMATION**

3 **WARNING: SERIOUS SKIN RASHES**

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

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

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

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

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

37 **1 INDICATIONS AND USAGE**

38 **1.1 Adjunctive Therapy**

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

42 **1.2 Monotherapy**

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

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

48 **1.3 Limitation of Use**

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

51 **2 DOSAGE AND ADMINISTRATION**

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

54 **2.1 General Dosing Considerations**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

170

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

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

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

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

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

182

183 **2.3 Conversion From Adjunctive Therapy to Monotherapy**

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

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

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

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

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

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

201

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

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

204

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

211 **2.4 Conversion From Immediate-Release Lamotrigine Tablets to LAMICTAL XR**

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

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

### 221 **3 DOSAGE FORMS AND STRENGTHS**

#### 222 **3.1 Extended-Release Tablets**

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

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

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

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

231 250 mg, purple with white center, caplet-shaped, film-coated tablets printed with  
232 “LAMICTAL” and “XR 250.”

233 300 mg, gray with white center, caplet-shaped, film-coated tablets printed with  
234 “LAMICTAL” and “XR 300.”

#### 235 **3.2 Potential Medication Errors**

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

### 240 **4 CONTRAINDICATIONS**

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

### 244 **5 WARNINGS AND PRECAUTIONS**

#### 245 **5.1 Serious Skin Rashes**

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

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

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

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

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

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

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

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

## 281 **5.2 Multiorgan Hypersensitivity Reactions and Organ Failure**

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

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

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

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

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

### 303 **5.3 Blood Dyscrasias**

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

### 308 **5.4 Suicidal Behavior and Ideation**

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

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

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

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

329 across a range of indications suggests that the risk applies to all AEDs used for any indication.  
330 The risk did not vary substantially by age (5 to 100 years) in the clinical trials analyzed.  
331 Table 3 shows absolute and relative risk by indication for all evaluated AEDs.  
332

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

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

334  
335 The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy  
336 than in clinical trials for psychiatric or other conditions, but the absolute risk differences were  
337 similar for the epilepsy and psychiatric indications.

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

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

### 349 **5.5 Aseptic Meningitis**

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

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

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

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

### 371 **5.6 Potential Medication Errors**

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

### 388 **5.7 Concomitant Use With Oral Contraceptives**

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

### 396 **5.8 Withdrawal Seizures**

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

400 at least 2 weeks (approximately 50% reduction per week) [*see Dosage and Administration*  
401 (2.1)].

## 402 **5.9 Status Epilepticus**

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

## 409 **5.10 Sudden Unexplained Death in Epilepsy**

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

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

## 428 **5.11 Addition of LAMICTAL XR to a Multidrug Regimen That Includes Valproate**

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

## 432 **5.12 Binding in the Eye and Other Melanin-Containing Tissues**

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

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

### 442 **5.13 Laboratory Tests**

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

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

## 454 **6 ADVERSE REACTIONS**

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

- 457 • Serious skin rashes [*see Warnings and Precautions (5.1)*]
- 458 • Multiorgan hypersensitivity reactions and organ failure [*see Warnings and Precautions (5.2)*]
- 459 • Blood dyscrasias [*see Warnings and Precautions (5.3)*]
- 460 • Suicidal behavior and ideation [*see Warnings and Precautions (5.4)*]
- 461 • Aseptic meningitis [*see Warnings and Precautions (5.5)*]
- 462 • Withdrawal seizures [*see Warnings and Precautions (5.8)*]
- 463 • Status epilepticus [*see Warnings and Precautions (5.9)*]
- 464 • Sudden unexplained death in epilepsy [*see Warnings and Precautions (5.10)*]

### 465 **6.1 Clinical Trial Experience With LAMICTAL XR for Treatment of Primary** 466 **Generalized Tonic-Clonic and Partial Onset Seizures**

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

471 LAMICTAL XR has been evaluated for safety in patients  $\geq 13$  years of age with PGTC  
472 and partial onset seizures. The most commonly observed adverse reactions in these 2 double-  
473 blind, placebo-controlled trials of adjunctive therapy with LAMICTAL XR were, in order of  
474 decreasing incidence (treatment difference between LAMICTAL XR and placebo  $\geq 4\%$ ):  
475 dizziness, tremor/intention tremor, vomiting, and diplopia.

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

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478 the most common reason for withdrawal in the group receiving LAMICTAL XR (5 patients  
479 [3%]). The next most common adverse reactions leading to withdrawal in 2 patients each (1%)  
480 were rash, headache, nausea, and nystagmus.

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

483

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

Body System/Adverse Reaction	LAMICTAL XR (n = 190) %	Placebo (n = 195) %
Ear and labyrinth disorders		
Vertigo	3	<1
Eye disorders		
Diplopia	5	<1
Vision blurred	3	2
Gastrointestinal disorders		
Nausea	7	4
Vomiting	6	3
Diarrhea	5	3
Constipation	2	<1
Dry mouth	2	1
General disorders and administration site conditions		
Asthenia and fatigue	6	4
Infections and infestations		
Sinusitis	2	1
Metabolic and nutritional disorders		
Anorexia	3	2
Musculoskeletal and connective tissue disorder		
Myalgia	2	0
Nervous system		
Dizziness	14	6
Tremor and intention tremor	6	1
Somnolence	5	3
Cerebellar coordination and balance disorder	3	0
Nystagmus	2	<1

Psychiatric disorders		
Depression	3	<1
Anxiety	3	0
Respiratory, thoracic, and mediastinal disorders		
Pharyngolaryngeal pain	3	2
Vascular disorder		
Hot flush	2	0

487 Note: In these trials the incidence of nonserious rash was 2% for LAMICTAL XR and 3% for  
488 placebo. In clinical trials evaluating immediate-release lamotrigine, the rate of serious rash was  
489 0.3% in adults on adjunctive therapy for epilepsy [*see Boxed Warning*].

490

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

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

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

511 *Monotherapy in Patients With Epilepsy:* Adverse reactions observed in this study  
512 were generally similar to those observed and attributed to drug in adjunctive and monotherapy  
513 immediate-release lamotrigine and adjunctive LAMICTAL XR placebo-controlled studies. Only  
514 2 adverse events, nasopharyngitis and upper respiratory tract infection, were observed at a rate of  
515  $\geq 3\%$  and not reported at a similar rate in previous studies. Because this study did not include a  
516 placebo control group, causality could not be established [*see Clinical Studies (14.3)*].

## 517 **6.2 Other Adverse Reactions Observed During the Clinical Development of** 518 **Immediate-Release Lamotrigine**

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

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

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

529 *Musculoskeletal:* Arthralgia.

530 *Nervous:* Insomnia, convulsion, irritability, speech disorder, concentration  
531 disturbance.

532 *Respiratory:* Pharyngitis, cough increased.

533 *Skin and Appendages:* Rash, pruritus.

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

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

541 *Body as a Whole:* Chest pain.

542 *Digestive:* Rectal hemorrhage, peptic ulcer.

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

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

545 *Respiratory:* Epistaxis, dyspnea.

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

547 *Special Senses:* Vision abnormality.

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

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

552 Adverse reactions are further classified within body system categories and enumerated in  
553 order of decreasing frequency using the following definitions: *frequent* adverse reactions are  
554 defined as those occurring in at least 1/100 patients; *infrequent* adverse reactions are those  
555 occurring in 1/100 to 1/1,000 patients; *rare* adverse reactions are those occurring in fewer than  
556 1/1,000 patients.

557 *Cardiovascular System: Infrequent:* Hypertension, palpitations, postural  
558 hypotension, syncope, tachycardia, vasodilation.

559 *Dermatological: Infrequent:* Acne, alopecia, hirsutism, maculopapular rash, urticaria.

560 *Rare:* Leukoderma, multiforme erythema, petechial rash, pustular rash.

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

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

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

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

571 *Musculoskeletal System: Rare:* Muscle atrophy, pathological fracture, tendinous  
572 contracture.

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

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

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

585 *Urogenital System: Infrequent:* Abnormal ejaculation, hematuria, impotence,  
586 menorrhagia, polyuria, urinary incontinence. *Rare:* Acute kidney failure, breast neoplasm,  
587 creatinine increase, female lactation, kidney failure, kidney pain, nocturia, urinary retention,  
588 urinary urgency.

### 589 **6.3 Postmarketing Experience With Immediate-Release Lamotrigine**

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

595 Blood and Lymphatic: Agranulocytosis, hemolytic anemia, lymphadenopathy not  
596 associated with hypersensitivity disorder.

597 Gastrointestinal: Esophagitis.

598 Hepatobiliary Tract and Pancreas: Pancreatitis.

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- 599            Immunologic: Lupus-like reaction, vasculitis.
- 600            Lower Respiratory: Apnea.
- 601            Musculoskeletal: Rhabdomyolysis has been observed in patients experiencing
- 602 hypersensitivity reactions.
- 603            Neurology: Exacerbation of Parkinsonian symptoms in patients with pre-existing
- 604 Parkinson's disease, tics.
- 605            Non-site Specific: Progressive immunosuppression.

606    **7        DRUG INTERACTIONS**

607            Significant drug interactions with lamotrigine are summarized in Table 5. Additional  
608 details of these drug interaction studies, which were conducted using immediate-release  
609 lamotrigine, are provided in the Clinical Pharmacology section [*see Clinical Pharmacology*  
610 (*12.3*)].

611  
612

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

Concomitant Drug	Effect on Concentration of Lamotrigine or Concomitant Drug	Clinical Comment
Estrogen-containing oral contraceptive preparations containing 30 mcg ethinylestradiol and 150 mcg levonorgestrel	↓ lamotrigine  ↓ levonorgestrel	Decreased lamotrigine levels approximately 50%.  Decrease in levonorgestrel component by 19%.
Carbamazepine and carbamazepine epoxide	↓ lamotrigine  ? CBZ epoxide	Addition of carbamazepine decreases lamotrigine concentration approximately 40%.  May increase carbamazepine epoxide levels.
Phenobarbital/Primidone	↓ lamotrigine	Decreased lamotrigine concentration approximately 40%.
Phenytoin	↓ lamotrigine	Decreased lamotrigine concentration approximately 40%.
Rifampin	↓ lamotrigine	Decreased lamotrigine AUC approximately 40%.
Valproate	↑ lamotrigine  ? valproate	Increased lamotrigine concentrations slightly more than 2-fold.  Decreased valproate concentrations an average of 25% over a 3-week period then

		stabilized in healthy volunteers; no change in controlled clinical trials in epilepsy patients.
--	--	---

613 ↓ = Decreased (induces lamotrigine glucuronidation).

614 ↑ = Increased (inhibits lamotrigine glucuronidation).

615 ? = Conflicting data.

## 616 **8 USE IN SPECIFIC POPULATIONS**

### 617 **8.1 Pregnancy**

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

622 Pregnancy Category C.

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

627 When lamotrigine was administered to pregnant mice, rats, or rabbits during the period of  
628 organogenesis (oral doses of up to 125, 25, and 30 mg/kg, respectively), reduced fetal body  
629 weight and increased incidences of fetal skeletal variations were seen in mice and rats at doses  
630 that were also maternally toxic. The no-effect doses for embryo-fetal developmental toxicity in  
631 mice, rats, and rabbits (75, 6.25, and 30 mg/kg, respectively) are similar to (mice and rabbits) or  
632 less than the human dose of 400 mg/day on a body surface area (mg/m<sup>2</sup>) basis.

633 In a study in which pregnant rats were administered lamotrigine (oral doses of 5 or 25  
634 mg/kg) during the period of organogenesis and offspring were evaluated postnatally, behavioral  
635 abnormalities were observed in exposed offspring at both doses. The lowest effect dose for  
636 developmental neurotoxicity in rats is less than the human dose of 400 mg/day on a mg/m<sup>2</sup> basis.  
637 Maternal toxicity was observed at the higher dose tested.

638 When pregnant rats were administered lamotrigine (oral doses of 5, 10, or 20 mg/kg)  
639 during the latter part of gestation, increased offspring mortality (including stillbirths) was seen at  
640 all doses. The lowest effect dose for peri/postnatal developmental toxicity in rats is less than the  
641 human dose of 400 mg/day on a mg/m<sup>2</sup> basis. Maternal toxicity was observed at the two highest  
642 doses tested.

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

645 Pregnancy Registry: To provide information regarding the effects of in utero exposure  
646 to LAMICTAL XR, physicians are advised to recommend that pregnant patients taking  
647 LAMICTAL XR enroll in the North American Antiepileptic Drug (NAAED) Pregnancy  
648 Registry. This can be done by calling the toll-free number 1-888-233-2334, and must be done by

649 patients themselves. Information on the registry can also be found at the website  
650 <http://www.aedpregnancyregistry.org>.

## 651 **8.2 Labor and Delivery**

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

## 653 **8.3 Nursing Mothers**

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

## 667 **8.4 Pediatric Use**

668 LAMICTAL XR is indicated as adjunctive therapy for PGTC and partial onset seizures  
669 with or without secondary generalization in patients  $\geq 13$  years of age. Safety and effectiveness of  
670 LAMICTAL XR for any use in patients less than 13 years of age have not been established.

671 Immediate-release lamotrigine is indicated for adjunctive therapy in patients  $\geq 2$  years of  
672 age for partial seizures, the generalized seizures of Lennox-Gastaut syndrome, and PGTC  
673 seizures.

674 Safety and efficacy of immediate-release lamotrigine, used as adjunctive treatment for  
675 partial seizures, were not demonstrated in a small, randomized, double-blind, placebo-controlled  
676 withdrawal study in very young pediatric patients (aged 1 to 24 months). Immediate-release  
677 lamotrigine was associated with an increased risk for infectious adverse reactions (lamotrigine  
678 37%, placebo 5%), and respiratory adverse reactions (lamotrigine 26%, placebo 5%). Infectious  
679 adverse reactions included bronchiolitis, bronchitis, ear infection, eye infection, otitis externa,  
680 pharyngitis, urinary tract infection, and viral infection. Respiratory adverse reactions included  
681 nasal congestion, cough, and apnea.

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

## 688 **8.5 Geriatric Use**

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

### 695 **8.6 Patients With Hepatic Impairment**

696 Experience in patients with hepatic impairment is limited. Based on a clinical  
697 pharmacology study with immediate-release lamotrigine in 24 patients with mild, moderate, and  
698 severe liver impairment [see *Clinical Pharmacology (12.3)*], the following general  
699 recommendations can be made. No dosage adjustment is needed in patients with mild liver  
700 impairment. Initial, escalation, and maintenance doses should generally be reduced by  
701 approximately 25% in patients with moderate and severe liver impairment without ascites and  
702 50% in patients with severe liver impairment with ascites. Escalation and maintenance doses  
703 may be adjusted according to clinical response [see *Dosage and Administration (2.1)*].

### 704 **8.7 Patients With Renal Impairment**

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

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

## 715 **10 OVERDOSAGE**

### 716 **10.1 Human Overdose Experience**

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

### 721 **10.2 Management of Overdose**

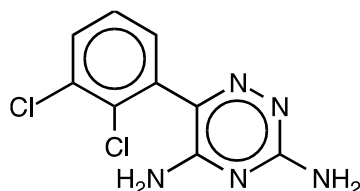
722 There are no specific antidotes for lamotrigine. Following a suspected overdose,  
723 hospitalization of the patient is advised. General supportive care is indicated, including frequent  
724 monitoring of vital signs and close observation of the patient. If indicated, emesis should be  
725 induced; usual precautions should be taken to protect the airway. It is uncertain whether  
726 hemodialysis is an effective means of removing lamotrigine from the blood. In 6 renal failure  
727 patients, about 20% of the amount of lamotrigine in the body was removed by hemodialysis

728 during a 4-hour session. A Poison Control Center should be contacted for information on the  
729 management of overdosage of LAMICTAL XR.

## 730 11 DESCRIPTION

731 LAMICTAL XR (lamotrigine), an AED of the phenyltriazine class, is chemically  
732 unrelated to existing AEDs. Its chemical name is 3,5-diamino-6-(2,3-dichlorophenyl)-*as*-triazine,  
733 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  
734 pale cream-colored powder and has a pK<sub>a</sub> of 5.7. Lamotrigine is very slightly soluble in water  
735 (0.17 mg/mL at 25°C) and slightly soluble in 0.1 M HCl (4.1 mg/mL at 25°C). The structural  
736 formula is:

737



738

739

740 LAMICTAL XR Extended-Release Tablets are supplied for oral administration as 25-mg  
741 (yellow with white center), 50-mg (green with white center), 100-mg (orange with white center),  
742 200-mg (blue with white center), 250-mg (purple with white center), and 300-mg (gray with  
743 white center) tablets. Each tablet contains the labeled amount of lamotrigine and the following  
744 inactive ingredients: glycerol monostearate, hypromellose, lactose monohydrate; magnesium  
745 stearate; methacrylic acid copolymer dispersion, polyethylene glycol 400, polysorbate 80, silicon  
746 dioxide (25- and 50-mg tablets only), titanium dioxide, triethyl citrate, carmine (250-mg tablet  
747 only), iron oxide black (50-, 250-, and 300-mg tablets only), iron oxide yellow (25-, 50-, and  
748 100-mg tablets only), iron oxide red (100-mg tablet only), FD&C Blue No. 2 Aluminum Lake  
749 (200- and 250-mg tablets only). Tablets are printed with edible black ink.

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

## 756 12 CLINICAL PHARMACOLOGY

### 757 12.1 Mechanism of Action

758 The precise mechanism(s) by which lamotrigine exerts its anticonvulsant action is  
759 unknown. In animal models designed to detect anticonvulsant activity, lamotrigine was effective  
760 in preventing seizure spread in the maximum electroshock and pentylenetetrazol tests, and  
761 prevented seizures in the visually and electrically evoked after-discharge tests for antiepileptic  
762 activity. Lamotrigine also displayed inhibitory properties in a kindling model in rats both during

763 kindling development and in the fully kindled state. The relevance of these models to human  
764 epilepsy, however, is not known.

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

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

771 Lamotrigine did not inhibit N-methyl d-aspartate (NMDA)-induced depolarizations in rat cortical  
772 slices or NMDA-induced cyclic GMP formation in immature rat cerebellum, nor did lamotrigine  
773 displace compounds that are either competitive or noncompetitive ligands at this glutamate  
774 receptor complex (CNQX, CGS, TCHP). The IC<sub>50</sub> for lamotrigine effects on NMDA-induced  
775 currents (in the presence of 3 μM of glycine) in cultured hippocampal neurons exceeded  
776 100 μM.

777 **12.2 Pharmacodynamics**

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

786 Cardiovascular: In dogs, lamotrigine is extensively metabolized to a 2-N-methyl  
787 metabolite. This metabolite causes dose-dependent prolongation of the PR interval, widening of  
788 the QRS complex, and, at higher doses, complete AV conduction block. Similar cardiovascular  
789 effects are not anticipated in humans because only trace amounts of the 2-N-methyl metabolite  
790 (<0.6% of lamotrigine dose) have been found in human urine [see *Clinical Pharmacology*  
791 *(12.3)*]. However, it is conceivable that plasma concentrations of this metabolite could be  
792 increased in patients with a reduced capacity to glucuronidate lamotrigine (e.g., in patients with  
793 liver disease, patients taking concomitant medications that inhibit glucuronidation).

794 **12.3 Pharmacokinetics**

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

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

801 In an open-label, crossover study of 44 subjects with epilepsy receiving concomitant  
802 AEDs, the steady-state pharmacokinetics of lamotrigine were compared following administration

803 of equivalent total doses of LAMICTAL XR given once daily with those of lamotrigine  
804 immediate-release given twice daily. In this study, the median time to peak concentration ( $T_{max}$ )  
805 following administration of LAMICTAL XR was 4 to 6 hours in patients taking carbamazepine,  
806 phenytoin, phenobarbital, or primidone; 9 to 11 hours in patients taking valproate; and 6 to 10  
807 hours in patients taking AEDs other than carbamazepine, phenytoin, phenobarbital, primidone,  
808 or valproate. In comparison, the median  $T_{max}$  following administration of immediate-release  
809 lamotrigine was between 1 and 1.5 hours.

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

826

827 **Table 6. Steady-State Bioavailability of LAMICTAL XR Relative to Immediate-Release**  
828 **Lamotrigine at Equivalent Daily Doses (Ratio of Extended-Release to Immediate-Release**  
829 **90% CI)**

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

830 <sup>a</sup> Enzyme-inducing antiepileptic drugs include carbamazepine, phenytoin, phenobarbital, and  
831 primidone.

832

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

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873 **Table 7. Mean<sup>a</sup> Pharmacokinetic Parameters of Immediate-Release Lamotrigine in**  
874 **Healthy Volunteers and Adult Patients With Epilepsy**

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

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

880 <sup>b</sup> Carbamazepine, phenobarbital, phenytoin, and primidone have been shown to increase the  
881 apparent clearance of lamotrigine. Estrogen-containing oral contraceptives and other drugs  
882 such as rifampin that induce lamotrigine glucuronidation have also been shown to increase  
883 the apparent clearance of lamotrigine [see *Drug Interactions (7)*].  
884

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

888 The net effects of drug interactions with lamotrigine are summarized in Table 8. Details  
889 of the drug interaction studies, which were done using immediate-release lamotrigine, are  
890 provided in Table 8.  
891

891  
892

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

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

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

- 894 <sup>b</sup> Net effects were estimated by comparing the mean clearance values obtained in adjunctive  
895 clinical trials and volunteer studies.
- 896 <sup>c</sup> The effect of other hormonal contraceptive preparations or hormone replacement therapy on  
897 the pharmacokinetics of lamotrigine has not been systematically evaluated in clinical trials,  
898 although the effect may be similar to that seen with the ethinylestradiol/levonorgestrel  
899 combinations.
- 900 <sup>d</sup> Modest decrease in levonorgestrel.
- 901 <sup>e</sup> Not administered, but an active metabolite of carbamazepine.
- 902 <sup>f</sup> Slight decrease, not expected to be clinically relevant.
- 903 <sup>g</sup> Not administered, but an active metabolite of oxcarbazepine.
- 904 <sup>h</sup> Slight increase, not expected to be clinically relevant.
- 905 ↔ = No significant effect.
- 906 ? = Conflicting data.
- 907

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

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

922 In the same study, coadministration of lamotrigine (300 mg/day) in 16 female volunteers  
923 did not affect the pharmacokinetics of the ethinylestradiol component of the oral contraceptive  
924 preparation. There were mean decreases in the AUC and  $C_{max}$  of the levonorgestrel component of  
925 19% and 12%, respectively. Measurement of serum progesterone indicated that there was no  
926 hormonal evidence of ovulation in any of the 16 volunteers, although measurement of serum  
927 FSH, LH, and estradiol indicated that there was some loss of suppression of the hypothalamic-  
928 pituitary-ovarian axis.

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

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

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

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

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

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

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

954 The addition of carbamazepine decreases lamotrigine steady-state concentrations by  
955 approximately 40%.

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

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

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

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

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

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

973            **Olanzapine:** The AUC and  $C_{\max}$  of olanzapine were similar following the addition of  
974 olanzapine (15 mg once daily) to lamotrigine (200 mg once daily) in healthy male volunteers (n  
975 = 16) compared with the AUC and  $C_{\max}$  in healthy male volunteers receiving olanzapine alone (n  
976 = 16).

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

981            **Oxcarbazepine:** The AUC and  $C_{\max}$  of oxcarbazepine and its active 10-monohydroxy  
982 oxcarbazepine metabolite were not significantly different following the addition of  
983 oxcarbazepine (600 mg twice daily) to lamotrigine (200 mg once daily) in healthy male  
984 volunteers (n = 13) compared with healthy male volunteers receiving oxcarbazepine alone  
985 (n = 13).

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

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

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

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

999            **Rifampin:** In 10 male volunteers, rifampin (600 mg/day for 5 days) significantly  
1000 increased the apparent clearance of a single 25-mg dose of lamotrigine by approximately 2-fold  
1001 (AUC decreased by approximately 40%).

1002            **Topiramate:** Topiramate resulted in no change in plasma concentrations of lamotrigine.  
1003 Administration of lamotrigine resulted in a 15% increase in topiramate concentrations.

1004            **Valproate:** When lamotrigine was administered to healthy volunteers (n = 18) receiving  
1005 valproate, the trough steady-state valproate plasma concentrations decreased by an average of  
1006 25% over a 3-week period, and then stabilized. However, adding lamotrigine to the existing  
1007 therapy did not cause a change in valproate plasma concentrations in either adult or pediatric  
1008 patients in controlled clinical trials.

1009            The addition of valproate increased lamotrigine steady-state concentrations in normal  
1010 volunteers by slightly more than 2-fold. In one study, maximal inhibition of lamotrigine  
1011 clearance was reached at valproate doses between 250 and 500 mg/day and did not increase as  
1012 the valproate dose was further increased.

1013 Zonisamide: In a study of 18 patients with epilepsy, coadministration of zonisamide  
1014 (200 to 400 mg/day) with lamotrigine (150 to 500 mg/day for 35 days) had no significant effect  
1015 on the pharmacokinetics of lamotrigine.

1016 Known Inducers or Inhibitors of Glucuronidation: Drugs other than those listed above  
1017 have not been systematically evaluated in combination with lamotrigine. Since lamotrigine is  
1018 metabolized predominately by glucuronic acid conjugation, drugs that are known to induce or  
1019 inhibit glucuronidation may affect the apparent clearance of lamotrigine, and doses of  
1020 LAMICTAL XR may require adjustment based on clinical response.

1021 Other: Results of in vitro experiments suggest that clearance of lamotrigine is unlikely to  
1022 be reduced by concomitant administration of amitriptyline, clonazepam, clozapine, fluoxetine,  
1023 haloperidol, lorazepam, phenelzine, risperidone, sertraline, or trazodone.

1024 Results of in vitro experiments suggest that lamotrigine does not reduce the clearance of  
1025 drugs eliminated predominantly by CYP2D6.

1026 Special Populations: Patients With Renal Impairment: Twelve volunteers with  
1027 chronic renal failure (mean creatinine clearance: 13 mL/min, range: 6 to 23) and another 6  
1028 individuals undergoing hemodialysis were each given a single 100-mg dose of immediate-release  
1029 lamotrigine. The mean plasma half-lives determined in the study were 42.9 hours (chronic renal  
1030 failure), 13.0 hours (during hemodialysis), and 57.4 hours (between hemodialysis) compared  
1031 with 26.2 hours in healthy volunteers. On average, approximately 20% (range: 5.6 to 35.1) of the  
1032 amount of lamotrigine present in the body was eliminated by hemodialysis during a 4-hour  
1033 session [*see Dosage and Administration (2.1)*].

1034 Hepatic Disease: The pharmacokinetics of lamotrigine following a single 100-mg  
1035 dose of immediate-release lamotrigine were evaluated in 24 subjects with mild, moderate, and  
1036 severe hepatic impairment (Child-Pugh Classification system) and compared with 12 subjects  
1037 without hepatic impairment. The patients with severe hepatic impairment were without ascites  
1038 (n = 2) or with ascites (n = 5). The mean apparent clearances of lamotrigine in patients with mild  
1039 (n = 12), moderate (n = 5), severe without ascites (n = 2), and severe with ascites (n = 5) liver  
1040 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,  
1041 as compared with  $0.37 \pm 0.1$  mL/min/kg in the healthy controls. Mean half-lives of lamotrigine  
1042 in patients with mild, moderate, severe without ascites, and severe with ascites hepatic  
1043 impairment were  $46 \pm 20$ ,  $72 \pm 44$ ,  $67 \pm 11$ , and  $100 \pm 48$  hours, respectively, as compared with  
1044  $33 \pm 7$  hours in healthy controls [*see Dosage and Administration (2.1)*].

1045 Elderly: The pharmacokinetics of lamotrigine following a single 150-mg dose of  
1046 immediate-release lamotrigine were evaluated in 12 elderly volunteers between the ages of 65  
1047 and 76 years (mean creatinine clearance: 61 mL/min, range: 33 to 108 mL/min). The mean half-  
1048 life of lamotrigine in these subjects was 31.2 hours (range: 24.5 to 43.4 hours), and the mean  
1049 clearance was 0.40 mL/min/kg (range: 0.26 to 0.48 mL/min/kg).

1050 Gender: The clearance of lamotrigine is not affected by gender. However, during  
1051 dose escalation of immediate-release lamotrigine in one clinical trial in patients with epilepsy on

1052 a stable dose of valproate (n = 77), mean trough lamotrigine concentrations, unadjusted for  
1053 weight, were 24% to 45% higher (0.3 to 1.7 mcg/mL) in females than in males.

1054 *Race:* The apparent oral clearance of lamotrigine was 25% lower in non-Caucasians  
1055 than Caucasians.

1056 *Pediatric Patients:* Safety and effectiveness of LAMICTAL XR for use in patients  
1057 less than 13 years of age have not been established.

## 1058 **13 NONCLINICAL TOXICOLOGY**

### 1059 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

1060 No evidence of carcinogenicity was seen in mouse or rat following oral administration of  
1061 lamotrigine for up to 2 years at doses up to 30 mg/kg/day and 10 to 15 mg/kg/day in mouse and  
1062 rat, respectively. The highest doses tested are less than the human dose of 400 mg/day on a body  
1063 surface area (mg/m<sup>2</sup>) basis.

1064 Lamotrigine was negative in *in vitro* gene mutation (Ames and mouse lymphoma *tk*)  
1065 assays and in clastogenicity (*in vitro* human lymphocyte and *in vivo* rat bone marrow) assays.

1066 No evidence of impaired fertility was detected in rats given oral doses of lamotrigine up  
1067 to 20 mg/kg/day. The highest dose tested is less than the human dose of 400 mg/day on a mg/m<sup>2</sup>  
1068 basis.

## 1069 **14 CLINICAL STUDIES**

### 1070 **14.1 Adjunctive Therapy for Primary Generalized Tonic-Clonic Seizures**

1071 The effectiveness of LAMICTAL XR as adjunctive therapy was established in PGTC  
1072 seizures in a 19-week, international, multicenter, double-blind, randomized, placebo-controlled  
1073 study in 143 patients 13 years of age and older (n = 70 on LAMICTAL XR and n = 73 on  
1074 placebo). Patients with at least 3 PGTC seizures during an 8-week baseline phase were  
1075 randomized to 19 weeks of treatment with LAMICTAL XR or placebo added to their current  
1076 AED regimen of up to 2 drugs. Patients were dosed on a fixed-dose regimen, with target doses  
1077 ranging from 200 to 500 mg/day of LAMICTAL XR based on concomitant AED(s) (target dose  
1078 = 200 mg for valproate, 300 mg for AEDs not altering plasma lamotrigine levels, and 500 mg for  
1079 enzyme-inducing AEDs).

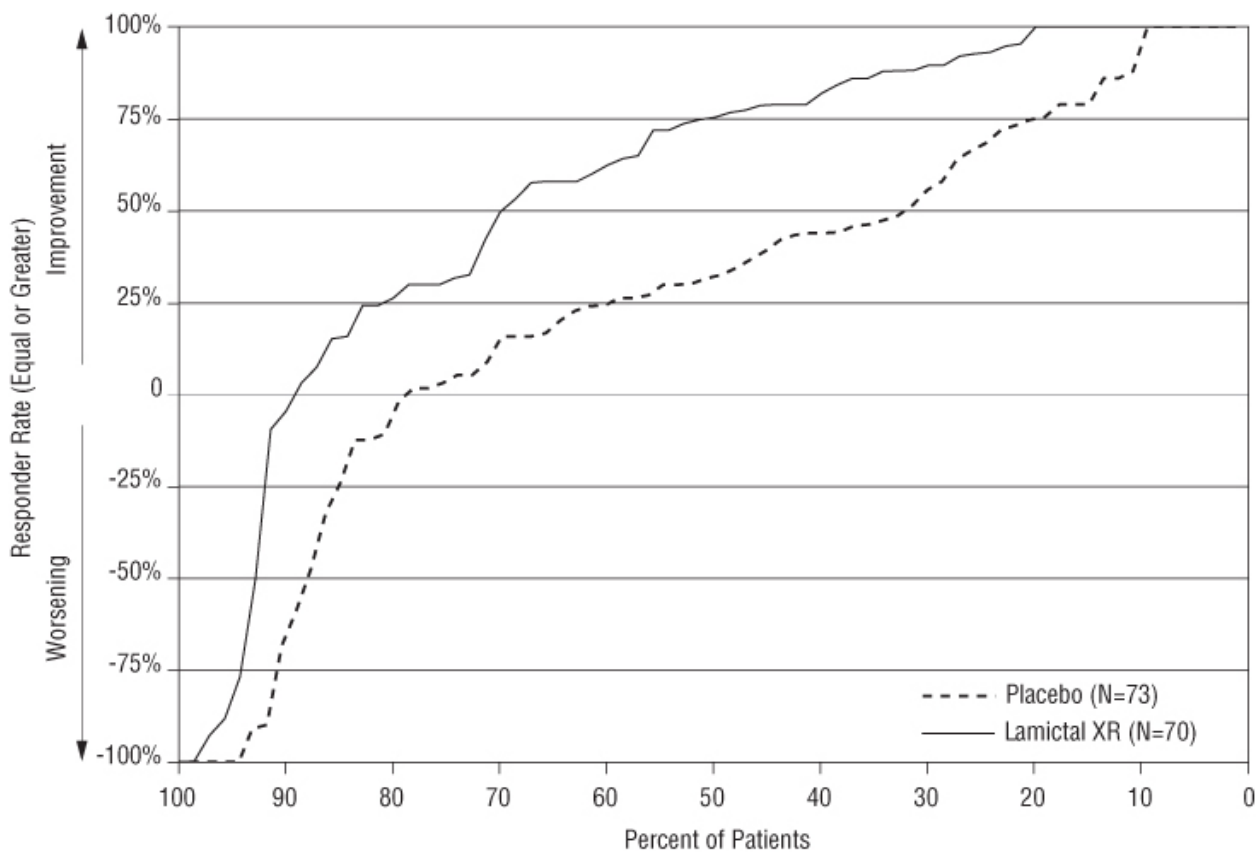
1080 The primary efficacy endpoint was percent change from baseline in PGTC seizure  
1081 frequency during the double-blind treatment phase. For the intent-to-treat population, the median  
1082 percent reduction in PGTC seizure frequency was 75% in patients treated with LAMICTAL XR  
1083 and 32% in patients treated with placebo, a difference that was statistically significant, defined as  
1084 a 2-sided *P* value  $\leq 0.05$ .

1085 Figure 1 presents the percentage of patients (X-axis) with a percent reduction in PGTC  
1086 seizure frequency (responder rate) from baseline through the entire treatment period at least as  
1087 great as that represented on the Y-axis. A positive value on the Y-axis indicates an improvement  
1088 from baseline (i.e., a decrease in seizure frequency), while a negative value indicates a worsening  
1089 from baseline (i.e., an increase in seizure frequency). Thus, in a display of this type, a curve for  
1090 an effective treatment is shifted to the left of the curve for placebo. The proportion of patients

1091 achieving any particular level of reduction in PGTC seizure frequency was consistently higher  
1092 for the group treated with LAMICTAL XR compared with the placebo group. For example, 70%  
1093 of patients randomized to LAMICTAL XR experienced a 50% or greater reduction in PGTC  
1094 seizure frequency, compared with 32% of patients randomized to placebo. Patients with an  
1095 increase in seizure frequency >100% are represented on the Y-axis as equal to or greater than  
1096 -100%.

1097

1098 **Figure 1. Proportion of Patients by Responder Rate for LAMICTAL XR and Placebo**  
1099 **Group (Primary Generalized Tonic-Clonic Seizures Study)**



1100

#### 1101 **14.2 Adjunctive Therapy for Partial Onset Seizures**

1102 The effectiveness of immediate-release lamotrigine as adjunctive therapy was initially  
1103 established in 3 pivotal, multicenter, placebo-controlled, double-blind clinical trials in 355 adults  
1104 with refractory partial onset seizures.

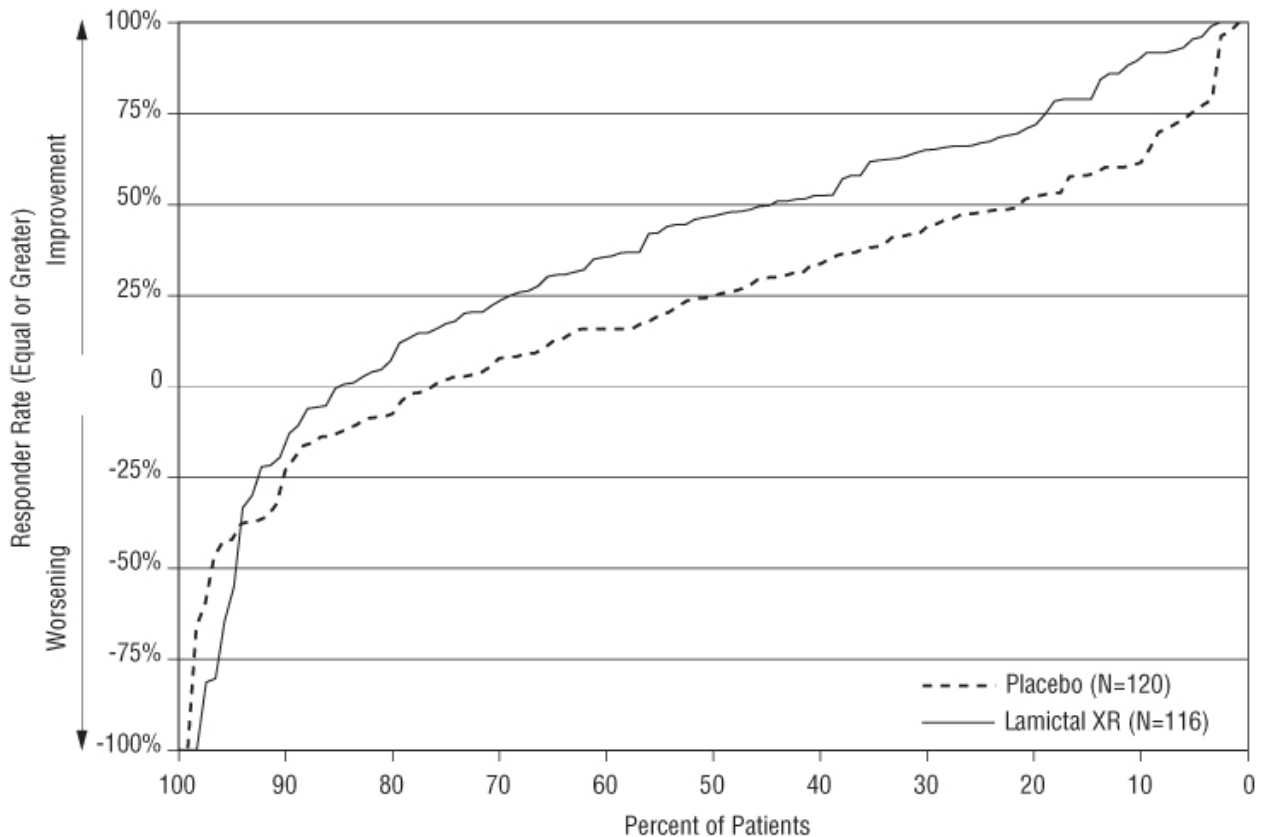
1105 The effectiveness of LAMICTAL XR as adjunctive therapy in partial onset seizures, with  
1106 or without secondary generalization, was established in a 19-week, multicenter, double-blind,  
1107 placebo-controlled trial in 236 patients 13 years of age and older (approximately 93% of patients  
1108 were aged 16 to 65 years). Approximately 36% were from the U.S. and approximately 64% were  
1109 from other countries including Argentina, Brazil, Chile, Germany, India, Korea, Russian  
1110 Federation, and Ukraine. Patients with at least 8 partial onset seizures during an 8-week  
1111 prospective baseline phase (or 4-week prospective baseline coupled with a 4-week historical

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1131 **Figure 2. Proportion of Patients by Responder Rate for LAMICTAL XR and Placebo**  
1132 **Group (Partial Onset Seizure Study)**



1133  
1134

### 1135 **14.3 Conversion to Monotherapy for Partial Onset Seizures**

1136 The effectiveness of LAMICTAL XR as monotherapy for partial onset seizures was  
1137 established in a historical-control trial in 223 adults with partial seizures. The historical control  
1138 methodology is described in a publication by French, et al. [see References (15)]. Briefly, in this  
1139 study, patients were randomized to ultimately receive either LAMICTAL XR 300 mg or 250 mg  
1140 once a day, and their responses were compared to those of a historical control group. The  
1141 historical control consisted of a pooled analysis of the control groups from 8 studies of similar  
1142 design, which utilized a subtherapeutic dose of an AED as a comparator. Statistical superiority to  
1143 the historical control was considered to be demonstrated if the upper 95% confidence interval for  
1144 the proportion of patients meeting escape criteria in patients receiving LAMICTAL XR remained  
1145 below the lower 95% prediction interval of 65.3% derived from the historical control data.

1146 In this study, patients  $\geq 13$  years of age experienced at least 4 partial seizures during an 8-  
1147 week baseline period with at least 2 seizures occurring during each of 2 consecutive 4-week  
1148 periods while receiving valproate or a non-enzyme-inducing AED. LAMICTAL XR was added  
1149 to either valproate or a non-enzyme-inducing AED over a 6- to 7-week period followed by the  
1150 gradual withdrawal of the background AED. Patients were then continued on monotherapy with  
1151 LAMICTAL XR for 12 weeks. The escape criteria were one or more of the following:

1152 (1) doubling of average monthly seizure count during any 28 consecutive days, (2) doubling of  
1153 highest consecutive 2-day seizure frequency during the entire treatment phase, (3) emergence of  
1154 a new seizure type compared to baseline (4) clinically significant prolongation of generalized  
1155 tonic-clonic seizures or worsening of seizure considered by the investigator to require  
1156 intervention. These criteria were similar to those in the 8 controlled trials from which the  
1157 historical control group was constituted.

1158 The upper 95% confidence limits of the proportion of subjects meeting escape criteria  
1159 (40.2% at 300 mg/day and 44.5% at 250 mg/day) were below the threshold of 65.3% derived  
1160 from the historical control data.

1161 Although the study population was not fully comparable to the historical controlled  
1162 population and the study was not fully blinded, numerous sensitivity analyses supported the  
1163 primary results. Efficacy was further supported by the established effectiveness of the  
1164 immediate-release formulation as monotherapy.

## 1165 **15 REFERENCES**

1166 1. French JA, Wang S, Warnock B, Temkin N. Historical control monotherapy design in the  
1167 treatment of epilepsy. *Epilepsia*. 2010; 51(10):1936-1943.

## 1168 **16 HOW SUPPLIED/STORAGE AND HANDLING**

### 1169 **LAMICTAL XR (lamotrigine) Extended-Release Tablets**

1170 25 mg, yellow with a white center, round, biconvex, film-coated tablets printed on one  
1171 face in black ink with "LAMICTAL" and "XR 25", unit-of-use bottles of 30 with orange caps  
1172 (NDC 0173-0754-00).

1173 50 mg, green with a white center, round, biconvex, film-coated tablets printed on one  
1174 face in black ink with "LAMICTAL" and "XR 50", unit-of-use bottles of 30 with orange caps  
1175 (NDC 0173-0755-00).

1176 100 mg, orange with a white center, round, biconvex, film-coated tablets printed on one  
1177 face in black ink with "LAMICTAL" and "XR 100", unit-of-use bottles of 30 with orange caps  
1178 (NDC 0173-0756-00).

1179 200 mg, blue with a white center, round, biconvex, film-coated tablets printed on one  
1180 face in black ink with "LAMICTAL" and "XR 200", unit-of-use bottles of 30 with orange caps  
1181 (NDC 0173-0757-00).

1182 250 mg, purple with a white center, caplet-shaped, film-coated tablets printed on one face  
1183 in black ink with "LAMICTAL" and "XR 250", unit-of-use bottles of 30 with orange caps (NDC  
1184 0173-0781-00).

1185 300 mg, gray with a white center, caplet-shaped, film-coated tablets printed on one face  
1186 in black ink with "LAMICTAL" and "XR 300", unit-of-use bottles of 30 with orange caps (NDC  
1187 0173-0761-00).

1188 **LAMICTAL XR (lamotrigine) Patient Titration Kit for Patients Taking Valproate**  
1189 **(Blue XR Kit)**

1190 25 mg, yellow with a white center, round, biconvex, film-coated tablets printed on one  
1191 face in black ink with “LAMICTAL” and “XR 25” and 50 mg, green with a white center, round,  
1192 biconvex, film-coated tablets printed on one face in black ink with “LAMICTAL” and “XR 50”;  
1193 blisterpack of 21/25-mg tablets and 7/50-mg tablets (NDC 0173-0758-00).

1194 **LAMICTAL XR (lamotrigine) Patient Titration Kit for Patients Taking**  
1195 **Carbamazepine, Phenytoin, Phenobarbital, or Primidone, and Not Taking Valproate**  
1196 **(Green XR Kit)**

1197 50 mg, green with a white center, round, biconvex, film-coated tablets printed on one  
1198 face in black ink with “LAMICTAL” and “XR 50”; 100 mg, orange with a white center, round,  
1199 biconvex, film-coated tablets printed on one face in black ink with “LAMICTAL” and “XR  
1200 100”; and 200 mg, blue with a white center, round, biconvex, film-coated tablets printed on one  
1201 face in black ink with “LAMICTAL” and “XR 200”; blisterpack of 14/50-mg tablets, 14/100-mg  
1202 tablets, and 7/200-mg tablets (NDC 0173-0759-00).

1203 **LAMICTAL XR (lamotrigine) Patient Titration Kit for Patients Not Taking**  
1204 **Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate (Orange XR Kit)**

1205 25 mg, yellow with a white center, round, biconvex, film-coated tablets printed on one  
1206 face in black ink with “LAMICTAL” and “XR 25”; 50 mg, green with a white center, round,  
1207 biconvex, film-coated tablets printed on one face in black ink with “LAMICTAL” and “XR 50”;  
1208 and 100 mg, orange with a white center, round, biconvex, film-coated tablets printed on one face  
1209 in black ink with “LAMICTAL” and “XR 100”; blisterpack of 14/25-mg tablets, 14/50-mg  
1210 tablets, and 7/100-mg tablets (NDC 0173-0760-00).

1211 **Storage:** Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP  
1212 Controlled Room Temperature].

1213 **17 PATIENT COUNSELING INFORMATION**

1214 *See FDA-approved patient labeling (Medication Guide).*

1215 **17.1 Rash**

1216 Prior to initiation of treatment with LAMICTAL XR, the patient should be instructed that  
1217 a rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy) may herald  
1218 a serious medical event and that the patient should report any such occurrence to a physician  
1219 immediately.

1220 **17.2 Multiorgan Hypersensitivity Reactions, Blood Dyscrasias and Organ**  
1221 **Failure**

1222 Patients should be instructed that multiorgan hypersensitivity reactions and acute  
1223 multiorgan failure may occur with LAMICTAL. Isolated organ failure or isolated blood  
1224 dyscrasias without evidence of multiorgan hypersensitivity may also occur. Patients should  
1225 contact their physician immediately if they experience any signs or symptoms of these conditions  
1226 [see *Warnings and Precautions (5.2, 5.3)*].

1227 **17.3 Suicidal Thinking and Behavior**

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1268 meningitis such as headache, fever, nausea, vomiting, stiff neck, rash, abnormal sensitivity to  
1269 light, myalgia, chills, confusion, or drowsiness while taking LAMICTAL XR.

1270 **17.10 Potential Medication Errors**

1271 Medication errors involving LAMICTAL have occurred. In particular the names  
1272 LAMICTAL or lamotrigine can be confused with the names of other commonly used  
1273 medications. Medication errors may also occur between the different formulations of  
1274 LAMICTAL. To reduce the potential of medication errors, write and say LAMICTAL XR  
1275 clearly. Depictions of the LAMICTAL XR Extended-Release Tablets can be found in the  
1276 Medication Guide. Each LAMICTAL XR tablet has a distinct color and white center, and is  
1277 printed with “LAMICTAL XR” and the tablet strength. These distinctive features serve to  
1278 identify the different presentations of the drug and thus may help reduce the risk of medication  
1279 errors. LAMICTAL XR is supplied in round, unit-of-use bottles with orange caps containing 30  
1280 tablets. The label on the bottle includes a depiction of the tablets that further communicates to  
1281 patients and pharmacists that the medication is LAMICTAL XR and the specific tablet strength  
1282 included in the bottle. The unit-of-use bottle with a distinctive orange cap and distinctive bottle  
1283 label features serves to identify the different presentations of the drug and thus may help to  
1284 reduce the risk of medication errors. **To avoid a medication error of using the wrong drug or  
1285 formulation, patients should be strongly advised to visually inspect their tablets to verify  
1286 that they are LAMICTAL XR each time they fill their prescription and to immediately talk  
1287 to their doctor/pharmacist if they receive a LAMICTAL XR tablet without a white center  
1288 and without “LAMICTAL XR” and the strength printed on the tablet as they may have  
1289 received the wrong medication [see Dosage Forms and Strengths (3), How Supplied/Storage  
1290 and Handling (16)].**

1291  
1292 LAMICTAL XR and DiffCORE are trademarks of GlaxoSmithKline.

1293  
1294



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1297 Research Triangle Park, NC 27709

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1300  
1301 Month Year  
1302 LXR:xPI

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1305 **MEDICATION GUIDE**

1306

1307

**LAMICTAL<sup>®</sup> (la-MIK-tal) XR<sup>™</sup> (lamotrigine) Extended-Release Tablets**

1308

1309

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

1313

1314

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

1315

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

1316

1317

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

1318

1319

1320

1321

1322

1323

The risk of getting a rash is higher if you:

1324

- take LAMICTAL XR while taking valproate [DEPAKENE (valproic acid) or DEPAKOTE (divalproex sodium)].

1325

1326

- take a higher starting dose of LAMICTAL XR than your healthcare provider prescribed.

1327

- increase your dose of LAMICTAL XR faster than prescribed.

1328

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

1329

1330

1331

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

1332

- a skin rash

1333

- hives

1334

- fever

1335

- swollen lymph glands

1336

- painful sores in the mouth or around your eyes

1337

- swelling of your lips or tongue

1338

- yellowing of your skin or eyes

1339

- unusual bruising or bleeding

1340

- severe fatigue or weakness

1341

- severe muscle pain

1342

- frequent infections

1343 These symptoms may be the first signs of a serious reaction. A healthcare provider should  
1344 examine you to decide if you should continue taking LAMICTAL XR.

1345 **2. Like other antiepileptic drugs, LAMICTAL XR may cause suicidal thoughts or actions**  
1346 **in a very small number of people, about 1 in 500.**

1347 **Call a healthcare provider right away if you have any of these symptoms, especially if**  
1348 **they are new, worse, or worry you:**

- 1349 • thoughts about suicide or dying
- 1350 • attempt to commit suicide
- 1351 • new or worse depression
- 1352 • new or worse anxiety
- 1353 • feeling agitated or restless
- 1354 • panic attacks
- 1355 • trouble sleeping (insomnia)
- 1356 • new or worse irritability
- 1357 • acting aggressive, being angry, or violent
- 1358 • acting on dangerous impulses
- 1359 • an extreme increase in activity and talking (mania)
- 1360 • other unusual changes in behavior or mood

1361 **Do not stop LAMICTAL XR without first talking to a healthcare provider.**

- 1362 • Stopping LAMICTAL XR suddenly can cause serious problems.
- 1363 • Suicidal thoughts or actions can be caused by things other than medicines. If you have  
1364 suicidal thoughts or actions, your healthcare provider may check for other causes.

1365 **How can I watch for early symptoms of suicidal thoughts and actions?**

- 1366 • Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or  
1367 feelings.
- 1368 • Keep all follow-up visits with your healthcare provider as scheduled.
- 1369 • Call your healthcare provider between visits as needed, especially if you are worried  
1370 about symptoms.

1371 **3. LAMICTAL XR may rarely cause aseptic meningitis, a serious inflammation of the**  
1372 **protective membrane that covers the brain and spinal cord.**

1373 **Call your healthcare provider right away if you have any of the following symptoms:**

- 1374 • Headache
- 1375 • Fever
- 1376 • Nausea
- 1377 • Vomiting
- 1378 • Stiff neck
- 1379 • Rash
- 1380 • Unusual sensitivity to light

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- 1381 • Muscle pains
- 1382 • Chills
- 1383 • Confusion
- 1384 • Drowsiness

1385 Meningitis has many causes other than LAMICTAL XR, which your doctor would check for  
1386 if you developed meningitis while taking LAMICTAL XR.

1387 **LAMICTAL XR can have other serious side effects.** For more information ask your  
1388 healthcare provider or pharmacist. Tell your healthcare provider if you have any side effect  
1389 that bothers you. Be sure to read the section below entitled “What are the possible side  
1390 effects of LAMICTAL XR?”

1391 **4. Patients prescribed LAMICTAL have sometimes been given the wrong medicine**  
1392 **because many medicines have names similar to LAMICTAL, so always check that you**  
1393 **receive LAMICTAL XR.**







1394 Taking the wrong medication can cause serious health problems. When your healthcare  
1395 provider gives you a prescription for LAMICTAL XR:

- 1396 • Make sure you can read it clearly.
- 1397 • Talk to your pharmacist to check that you are given the correct medicine.
- 1398 • Each time you fill your prescription, check the tablets you receive against the pictures of  
1399 the tablets below.

1400 These pictures show the distinct wording, colors, and shapes of the tablets that help to  
1401 identify the right strength of LAMICTAL XR. Immediately call your pharmacist if you  
1402 receive a LAMICTAL XR tablet that does not look like one of the tablets shown below, as  
1403 you may have received the wrong medication.

1404  
1405

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

 <b>25 mg, yellow with white center</b>  <b>Imprinted with LAMICTAL XR 25</b>	 <b>50 mg, green with white center</b>  <b>Imprinted with LAMICTAL XR 50</b>	 <b>100 mg, orange with white center</b>  <b>Imprinted with LAMICTAL XR 100</b>
 <b>200 mg, blue with white center</b>  <b>Imprinted with</b>	 <b>250 mg, purple with white center</b>  <b>Imprinted with</b>	 <b>300 mg, gray with white center</b>  <b>Imprinted with</b>

<b>LAMICTAL XR 200</b>	<b>LAMICTAL XR 250</b>	<b>LAMICTAL XR 300</b>
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1406

1407 **What is LAMICTAL XR?**

1408 LAMICTAL XR is a prescription medicine used:

- 1409 • together with other medicines to treat primary generalized tonic-clonic seizures and partial  
1410 onset seizures in people 13 years of age and older.  
1411 • alone to treat partial seizures when changing from certain other medicines used in people 13  
1412 years and older.

1413 It is not known if LAMICTAL XR is safe or effective in children less than 13 years of age. Other  
1414 forms of lamotrigine can be used in children aged 2 to 12 years.

1415

1416 **Who should not take LAMICTAL XR?**

1417 You should not take LAMICTAL XR if you have had an allergic reaction to lamotrigine or to  
1418 any of the inactive ingredients in LAMICTAL XR. See the end of this leaflet for a complete list  
1419 of ingredients in LAMICTAL XR.

1420

1421 **What should I tell my healthcare provider before taking LAMICTAL XR?**

1422 Before taking LAMICTAL XR, tell your healthcare provider about all of your medical  
1423 conditions, including if you:

- 1424 • have had a rash or allergic reaction to another antiseizure medicine.  
1425 • have or have had depression, mood problems, or suicidal thoughts or behavior.  
1426 • are taking oral contraceptives (birth control pills) or other female hormonal medicines. Do  
1427 not start or stop taking birth control pills or other female hormonal medicine until you have  
1428 talked with your healthcare provider. Tell your healthcare provider if you have any changes  
1429 in your menstrual pattern such as breakthrough bleeding. Stopping these medicines may  
1430 cause side effects (such as dizziness, lack of coordination, or double vision). Starting these  
1431 medicines may lessen how well LAMICTAL XR works.  
1432 • are pregnant or plan to become pregnant. It is not known if LAMICTAL XR will harm your  
1433 unborn baby. If you become pregnant while taking LAMICTAL XR, talk to your healthcare  
1434 provider about registering with the North American Antiepileptic Drug Pregnancy Registry.  
1435 You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to  
1436 collect information about the safety of antiepileptic drugs during pregnancy.  
1437 • are breastfeeding. LAMICTAL XR passes into breast milk and may cause side effects in a  
1438 breastfed baby. If you breastfeed while taking LAMICTAL XR, watch your baby closely for  
1439 trouble breathing, episodes of temporarily stopping breathing, sleepiness, or poor sucking.  
1440 Call your baby's healthcare provider right away if you see any of these problems. Talk to  
1441 your healthcare provider about the best way to feed your baby if you take LAMICTAL XR.

1442 Tell your healthcare provider about all the medicines you take or if you are planning to take a  
1443 new medicine, including prescription and non-prescription medicines, vitamins, and herbal  
1444 supplements. Using LAMICTAL XR with certain other medicines can affect each other, causing  
1445 side effects.

1446

1447 **How should I take LAMICTAL XR?**

- 1448 • Take LAMICTAL XR exactly as prescribed.
- 1449 • Your healthcare provider may change your dose. Do not change your dose without talking to  
1450 your healthcare provider.
- 1451 • Do not stop taking LAMICTAL XR without talking to your healthcare provider. Stopping  
1452 LAMICTAL XR suddenly may cause serious problems. For example, if you have epilepsy  
1453 and you stop taking LAMICTAL XR suddenly, you may get seizures that do not stop. Talk  
1454 with your healthcare provider about how to stop LAMICTAL XR slowly.
- 1455 • If you miss a dose of LAMICTAL XR, take it as soon as you remember. If it is almost time  
1456 for your next dose, just skip the missed dose. Take the next dose at your regular time. **Do not**  
1457 **take 2 doses at the same time.**
- 1458 • If you take too much LAMICTAL XR, call your healthcare provider or your local Poison  
1459 Control Center or go to the nearest hospital emergency room right away.
- 1460 • You may not feel the full effect of LAMICTAL XR for several weeks.
- 1461 • If you have epilepsy, tell your healthcare provider if your seizures get worse or if you have  
1462 any new types of seizures.
- 1463 • LAMICTAL XR can be taken with or without food.
- 1464 • Do not chew, crush, or divide LAMICTAL XR.
- 1465 • Swallow LAMICTAL XR tablets whole.
- 1466 • If you have trouble swallowing LAMICTAL XR Tablets, tell your healthcare provider  
1467 because there may be another form of lamotrigine you can take.
- 1468 • If you receive LAMICTAL XR in a blisterpack, examine the blisterpack before use. Do not  
1469 use if blisters are torn, broken, or missing.

1470

1471 **What should I avoid while taking LAMICTAL XR?**

1472 Do not drive a car or operate complex, hazardous machinery until you know how LAMICTAL  
1473 XR affects you.

1474

1475 **What are possible side effects of LAMICTAL XR?**

- 1476 • See “What is the most important information I should know about LAMICTAL XR?”  
1477 Common side effects of LAMICTAL XR include:
- 1478 • Dizziness
- 1479 • Tremor
- 1480 • Double vision

- 1481 • Nausea
- 1482 • Vomiting
- 1483 • Trouble with balance and coordination
- 1484 • Anxiety

1485 Other common side effects that have been reported with another form of lamotrigine include  
1486 headache, sleepiness, blurred vision, runny nose, and rash.

1487 Tell your healthcare provider about any side effect that bothers you or that does not go away.  
1488 These are not all the possible side effects of LAMICTAL XR. For more information, ask your  
1489 healthcare provider or pharmacist.

1490 Call your doctor for medical advice about side effects. You may report side effects to FDA at  
1491 1-800-FDA-1088.

1492

#### 1493 **How should I store LAMICTAL XR?**

- 1494 • Store LAMICTAL XR at room temperature between 59°F to 86°F (15°C to 30°C).
- 1495 • **Keep LAMICTAL XR and all medicines out of the reach of children.**

1496

#### 1497 **General information about LAMICTAL XR**

1498 Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.  
1499 Do not use LAMICTAL XR for a condition for which it was not prescribed. Do not give  
1500 LAMICTAL XR to other people, even if they have the same symptoms you have. It may harm  
1501 them.

1502 This Medication Guide summarizes the most important information about LAMICTAL XR. If  
1503 you would like more information, talk with your healthcare provider. You can ask your  
1504 healthcare provider or pharmacist for information about LAMICTAL XR that is written for  
1505 healthcare professionals.

1506 For more information, go to [www.lamictalxr.com](http://www.lamictalxr.com) or call 1-888-825-5249.

1507

#### 1508 **What are the ingredients in LAMICTAL XR?**

1509 Active ingredient: Lamotrigine.

1510 Inactive ingredients: glycerol monostearate, hypromellose, lactose monohydrate, magnesium  
1511 stearate, methacrylic acid copolymer dispersion, polyethylene glycol 400, polysorbate 80, silicon  
1512 dioxide (25- and 50-mg tablets only), titanium dioxide, triethyl citrate, carmine (250-mg tablet  
1513 only), iron oxide black (50-, 250-, and 300-mg tablets only), iron oxide yellow (25-, 50-, 100-mg  
1514 tablets only), iron oxide red (100-mg tablet only), FD&C Blue No. 2 Aluminum Lake (200- and  
1515 250-mg tablets only). Tablets are printed with edible black ink.

1516

1517 **This Medication Guide has been approved by the U.S. Food and Drug Administration.**

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1518

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