

NDA 20-241/S-003 & NDA 20-764/S-001

Approved Labeling Text

1 **LAMICTAL<sup>®</sup>**  
2 **(lamotrigine)**  
3 **Tablets**

PRODUCT INFORMATION

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5 **LAMICTAL<sup>®</sup>**  
6 **(lamotrigine)**  
7 **Chewable Dispersible Tablets**  
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9 **SERIOUS RASHES REQUIRING HOSPITALIZATION AND DISCONTINUATION OF**  
10 **TREATMENT HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF LAMICTAL. THE**  
11 **INCIDENCE OF THESE RASHES, WHICH HAVE INCLUDED STEVENS-JOHNSON SYNDROME,**  
12 **IS APPROXIMATELY 1% (1/100) IN PEDIATRIC PATIENTS (AGE <16 YEARS) AND 0.3%**  
13 **(3/1000) IN ADULTS. IN WORLDWIDE POSTMARKETING EXPERIENCE, RARE CASES OF**  
14 **TOXIC EPIDERMAL NECROLYSIS AND/OR RASH-RELATED DEATH HAVE BEEN REPORTED,**  
15 **BUT THEIR NUMBERS ARE TOO FEW TO PERMIT A PRECISE ESTIMATE OF THE RATE.**

16 **BECAUSE THE RATE OF SERIOUS RASH IS GREATER IN PEDIATRIC PATIENTS THAN IN**  
17 **ADULTS, IT BEARS EMPHASIS THAT LAMICTAL IS APPROVED ONLY FOR USE IN**  
18 **PEDIATRIC PATIENTS BELOW THE AGE OF 16 YEARS WHO HAVE SEIZURES ASSOCIATED**  
19 **WITH THE LENNOX-GASTAUT SYNDROME (SEE INDICATIONS).**

20 **OTHER THAN AGE, THERE ARE AS YET NO FACTORS IDENTIFIED THAT ARE KNOWN TO**  
21 **PREDICT THE RISK OF OCCURRENCE OR THE SEVERITY OF RASH ASSOCIATED WITH**  
22 **LAMICTAL. THERE ARE SUGGESTIONS, YET TO BE PROVEN, THAT THE RISK OF RASH**  
23 **MAY ALSO BE INCREASED BY 1) COADMINISTRATION OF LAMICTAL WITH VALPROIC ACID**  
24 **(VPA), 2) EXCEEDING THE RECOMMENDED INITIAL DOSE OF LAMICTAL, OR 3) EXCEEDING**  
25 **THE RECOMMENDED DOSE ESCALATION FOR LAMICTAL. HOWEVER, CASES HAVE BEEN**  
26 **REPORTED IN THE ABSENCE OF THESE FACTORS.**

27 **NEARLY ALL CASES OF LIFE-THREATENING RASHES ASSOCIATED WITH LAMICTAL**  
28 **HAVE OCCURRED WITHIN 2 TO 8 WEEKS OF TREATMENT INITIATION. HOWEVER,**  
29 **ISOLATED CASES HAVE BEEN REPORTED AFTER PROLONGED TREATMENT (e.g.,**  
30 **6 MONTHS). ACCORDINGLY, DURATION OF THERAPY CANNOT BE RELIED UPON AS A**  
31 **MEANS TO PREDICT THE POTENTIAL RISK HERALDED BY THE FIRST APPEARANCE OF A**  
32 **RASH.**

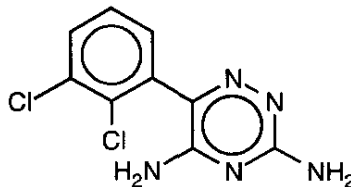
33 **ALTHOUGH BENIGN RASHES ALSO OCCUR WITH LAMICTAL, IT IS NOT POSSIBLE TO**  
34 **PREDICT RELIABLY WHICH RASHES WILL PROVE TO BE SERIOUS OR LIFE THREATENING.**  
35 **ACCORDINGLY, LAMICTAL SHOULD ORDINARILY BE DISCONTINUED AT THE FIRST SIGN**  
36 **OF RASH, UNLESS THE RASH IS CLEARLY NOT DRUG RELATED. DISCONTINUATION OF**  
37 **TREATMENT MAY NOT PREVENT A RASH FROM BECOMING LIFE THREATENING OR**  
38 **PERMANENTLY DISABLING OR DISFIGURING.**

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

40 **DESCRIPTION:** LAMICTAL (lamotrigine), an antiepileptic drug (AED) of the phenyltriazine class, is  
41 chemically unrelated to existing antiepileptic drugs. Its chemical name is 3,5-diamino-6-(2,3-  
42 dichlorophenyl)-as-triazine, its molecular formula is  $C_9H_7N_5Cl_2$ , and its molecular weight is 256.09.  
43 Lamotrigine is a white to pale cream-colored powder and has a  $pK_a$  of 5.7. Lamotrigine is very slightly  
44 soluble in water (0.17 mg/mL at 25°C) and slightly soluble in 0.1 M HCl (4.1 mg/mL at 25°C). The  
45 structural formula is:

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

54 LAMICTAL Chewable Dispersible Tablets are supplied for oral administration. The tablets contain  
55 5 mg (white) or 25 mg (white) of lamotrigine and the following inactive ingredients: blackcurrant flavor,  
56 calcium carbonate, low-substituted hydroxypropylcellulose, magnesium aluminum silicate,  
57 magnesium stearate, povidone, saccharin sodium, and sodium starch glycolate.

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59 **CLINICAL PHARMACOLOGY:**

60 **Mechanism of Action:** The precise mechanism(s) by which lamotrigine exerts its anticonvulsant  
61 action are unknown. In animal models designed to detect anticonvulsant activity, lamotrigine was  
62 effective in preventing seizure spread in the maximum electroshock (MES) and pentylenetetrazol  
63 (scMet) tests, and prevented seizures in the visually and electrically evoked after-discharge (EEAD)  
64 tests for antiepileptic activity. The relevance of these models to human epilepsy, however, is not  
65 known.

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

71 **Pharmacological Properties:** Although the relevance for human use is unknown, the following data  
72 characterize the performance of LAMICTAL in receptor binding assays. Lamotrigine had a weak  
73 inhibitory effect on the serotonin 5-HT<sub>3</sub> receptor ( $IC_{50} = 18 \mu M$ ). It does not exhibit high affinity binding  
74 ( $IC_{50} > 100 \mu M$ ) to the following neurotransmitter receptors: adenosine A<sub>1</sub> and A<sub>2</sub>; adrenergic  $\alpha_1$ ,  $\alpha_2$ ,  
75 and  $\beta$ ; dopamine D<sub>1</sub> and D<sub>2</sub>;  $\gamma$ -aminobutyric acid (GABA) A and B; histamine H<sub>1</sub>; kappa opioid;  
76 muscarinic acetylcholine; and serotonin 5-HT<sub>2</sub>. Studies have failed to detect an effect of lamotrigine

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77 on dihydropyridine-sensitive calcium channels. It had weak effects at sigma opioid receptors  
78 ( $IC_{50} = 145 \mu M$ ). Lamotrigine did not inhibit the uptake of norepinephrine, dopamine, serotonin, or  
79 aspartic acid ( $IC_{50} > 100 \mu M$ ).

80 **Effect of Lamotrigine on N-Methyl d-Aspartate (NMDA)-Mediated Activity:** Lamotrigine did  
81 not inhibit NMDA-induced depolarizations in rat cortical slices or NMDA-induced cyclic GMP  
82 formation in immature rat cerebellum, nor did lamotrigine displace compounds that are either  
83 competitive or noncompetitive ligands at this glutamate receptor complex (CNQX, CGS, TCHP). The  
84  $IC_{50}$  for lamotrigine effects on NMDA-induced currents (in the presence of  $3 \mu M$  of glycine) in cultured  
85 hippocampal neurons exceeded  $100 \mu M$ .

86 **Folate Metabolism:** In vitro, lamotrigine was shown to be an inhibitor of dihydrofolate reductase,  
87 the enzyme that catalyzes the reduction of dihydrofolate to tetrahydrofolate. Inhibition of this enzyme  
88 may interfere with the biosynthesis of nucleic acids and proteins. When oral daily doses of  
89 lamotrigine were given to pregnant rats during organogenesis, fetal, placental, and maternal folate  
90 concentrations were reduced. Significantly reduced concentrations of folate are associated with  
91 teratogenesis (see PRECAUTIONS: Pregnancy). Folate concentrations were also reduced in male  
92 rats given repeated oral doses of lamotrigine. Reduced concentrations were partially returned to  
93 normal when supplemented with folic acid.

94 **Accumulation in Kidneys:** Lamotrigine was found to accumulate in the kidney of the male rat,  
95 causing chronic progressive nephrosis, necrosis, and mineralization. These findings are attributed to  
96  $\alpha$ -2 microglobulin, a species- and sex-specific protein that has not been detected in humans or other  
97 animal species.

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

100 **Cardiovascular:** In dogs, lamotrigine is extensively metabolized to a 2-N-methyl metabolite. This  
101 metabolite causes dose-dependent prolongations of the PR interval, widening of the QRS complex,  
102 and, at higher doses, complete AV conduction block. Similar cardiovascular effects are not  
103 anticipated in humans because only trace amounts of the 2-N-methyl metabolite (<0.6% of  
104 lamotrigine dose) have been found in human urine (see Drug Disposition below). However, it is  
105 conceivable that plasma concentrations of this metabolite could be increased in patients with a  
106 reduced capacity to glucuronidate lamotrigine (e.g., in patients with liver disease).

107 **Pharmacokinetics and Drug Metabolism:** The pharmacokinetics of lamotrigine have been studied  
108 in patients with epilepsy, healthy young and elderly volunteers, and volunteers with chronic renal  
109 failure. Lamotrigine pharmacokinetic parameters for adult and pediatric patients and healthy normal  
110 volunteers are summarized in Tables 1 and 2.

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**Table 1: Mean\* Pharmacokinetic Parameters in Adult Patients  
With Epilepsy or Healthy Volunteers**

Adult Study Population	Number of Subjects	$t_{max}$ : Time of Maximum Plasma Concentration (h)	$t_{1/2}$ : Elimination Half-life (h)	Cl/F: Apparent Plasma Clearance (mL/min/kg)
Patients taking enzyme-inducing antiepileptic drugs (EIAEDs) <sup>†</sup> :				
Single-dose LAMICTAL	24	2.3 (0.5-5.0)	14.4 (6.4-30.4)	1.10 (0.51-2.22)
Multiple-dose LAMICTAL	17	2.0 (0.75-5.93)	12.6 (7.5-23.1)	1.21 (0.66-1.82)
Patients taking EIAEDs + VPA:				
Single-dose LAMICTAL	25	3.8 (1.0-10.0)	27.2 (11.2-51.6)	0.53 (0.27-1.04)
Patients taking VPA only:				
Single-dose LAMICTAL	4	4.8 (1.8-8.4)	58.8 (30.5-88.8)	0.28 (0.16-0.40)
Healthy volunteers taking VPA:				
Single-dose LAMICTAL	6	1.8 (1.0-4.0)	48.3 (31.5-88.6)	0.30 (0.14-0.42)
Multiple-dose LAMICTAL	18	1.9 (0.5-3.5)	70.3 (41.9-113.5)	0.18 (0.12-0.33)
Healthy volunteers taking no other medications:				
Single-dose LAMICTAL	179	2.2 (0.25-12.0)	32.8 (14.0-103.0)	0.44 (0.12-1.10)
Multiple-dose LAMICTAL	36	1.7 (0.5-4.0)	25.4 (11.6-61.6)	0.58 (0.24-1.15)

\*The majority of parameter means determined in each study had coefficients of variation between 20% and 40% for half-life and Cl/F and between 30% and 70% for  $t_{max}$ . The overall mean values were calculated from individual study means that were weighted based on the number of volunteers/patients in each study. The numbers in parentheses below each parameter mean represent the range of individual volunteer/patient values across studies.

<sup>†</sup>Examples of EIAEDs are carbamazepine, phenobarbital, phenytoin, and primidone.

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**The apparent clearance of lamotrigine is affected by the coadministration of AEDs.**

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123 Lamotrigine is eliminated more rapidly in patients who have been taking hepatic EIAEDs, including  
124 carbamazepine, phenytoin, phenobarbital, and primidone. Most clinical experience is derived from  
125 this population.

126 **VPA, however, actually decreases the apparent clearance of lamotrigine (i.e., more than**  
127 **doubles the elimination half-life of lamotrigine), whether given with or without EIAEDs.**

128 Accordingly, if lamotrigine is to be administered to a patient receiving VPA, lamotrigine must be given  
129 at a reduced dosage, less than half the dose used in patients not receiving VPA (see DOSAGE AND  
130 ADMINISTRATION and PRECAUTIONS: Drug Interactions).

131 **Absorption:** Lamotrigine is rapidly and completely absorbed after oral administration with  
132 negligible first-pass metabolism (absolute bioavailability is 98%). The bioavailability is not affected by  
133 food. Peak plasma concentrations occur anywhere from 1.4 to 4.8 hours following drug  
134 administration. The lamotrigine chewable/dispersible tablets were found to be equivalent, whether  
135 they were administered as dispersed in water, chewed and swallowed, or swallowed as whole, to the  
136 lamotrigine compressed tablets in terms of rate and extent of absorption.

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

140 **Protein Binding:** Data from in vitro studies indicate that lamotrigine is approximately 55% bound  
141 to human plasma proteins at plasma lamotrigine concentrations from 1 to 10 mcg/mL (10 mcg/mL is  
142 four to six times the trough plasma concentration observed in the controlled efficacy trials). Because  
143 lamotrigine is not highly bound to plasma proteins, clinically significant interactions with other drugs  
144 through competition for protein binding sites are unlikely. The binding of lamotrigine to plasma  
145 proteins did not change in the presence of therapeutic concentrations of phenytoin, phenobarbital, or  
146 VPA. Lamotrigine did not displace other AEDs (carbamazepine, phenytoin, phenobarbital) from  
147 protein binding sites.

148 **Drug Disposition:** Lamotrigine is metabolized predominantly by glucuronic acid conjugation; the  
149 major metabolite is an inactive 2-N-glucuronide conjugate. After oral administration of 240 mg of  
150 <sup>14</sup>C-lamotrigine (15 μCi) to six healthy volunteers, 94% was recovered in the urine and 2% was  
151 recovered in the feces. The radioactivity in the urine consisted of unchanged lamotrigine (10%), the  
152 2-N-glucuronide (76%), a 5-N-glucuronide (10%), a 2-N-methyl metabolite (0.14%), and other  
153 unidentified minor metabolites (4%).

154 **Enzyme Induction:** The effects of lamotrigine on specific families of mixed-function oxidase  
155 isozymes have not been systematically evaluated.

156 Following multiple administrations (150 mg twice daily) to normal volunteers taking no other  
157 medications, lamotrigine induced its own metabolism, resulting in a 25% decrease in T<sub>1/2</sub> and a 37%  
158 increase in Cl/F at steady state compared to values obtained in the same volunteers following a  
159 single dose. Evidence gathered from other sources suggests that self-induction by LAMICTAL may  
160 not occur when LAMICTAL is given as adjunctive therapy in patients receiving EIAEDs.

161 **Dose Proportionality:** In healthy volunteers not receiving any other medications and given single  
162 doses, the plasma concentrations of lamotrigine increased in direct proportion to the dose

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163 administered over the range of 50 to 400 mg. In two small studies (n = 7 and 8) of patients with  
164 epilepsy who were maintained on other AEDs, there also was a linear relationship between dose and  
165 lamotrigine plasma concentrations at steady state following doses of 50 to 350 mg twice daily.

166 **Elimination:** (See Table 1)

167 **Special Populations: Patients With Renal Insufficiency:** Twelve volunteers with chronic renal  
168 failure (mean creatinine clearance = 13 mL/min; range = 6 to 23) and another six individuals  
169 undergoing hemodialysis were each given a single 100-mg dose of LAMICTAL. The mean plasma  
170 half-lives determined in the study were 42.9 hours (chronic renal failure), 13.0 hours (during  
171 hemodialysis), and 57.4 hours (between hemodialysis) compared to 26.2 hours in healthy volunteers.  
172 On average, approximately 20% (range = 5.6 to 35.1) of the amount of lamotrigine present in the  
173 body was eliminated by hemodialysis during a 4-hour session.

174 **Hepatic Disease:** The pharmacokinetic parameters of lamotrigine in patients with impaired  
175 liver function have not been studied.

176 **Age: Pediatric Patients:** The pharmacokinetics of LAMICTAL following a single 2-mg/kg dose  
177 were evaluated in two studies of pediatric patients with epilepsy (n = 25 for patients aged 10 months  
178 to 5.3 years and n = 19 for patients aged 5 to 11 years). All patients were receiving concomitant  
179 therapy with other AEDs. Lamotrigine pharmacokinetic parameters for pediatric patients are  
180 summarized in Table 2.

181 As with adults, the elimination of lamotrigine in pediatric patients was similarly affected by  
182 concomitant AEDs. Weight normalized oral clearance (Cl/F) was higher (onefold to threefold) in  
183 infants and children (age 10 months to 11 years) than in the adolescents and adults, while  
184 adolescents and adults had similar mean values of Cl/F.

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**Table 2: Mean Pharmacokinetic Parameters in Pediatric Patients With Epilepsy**

Pediatric Study Population	Number of Subjects	t <sub>max</sub> (h)	t <sub>½</sub> (h)	Cl/F (mL/min/kg)
<b>Ages 10 months-5.3 years</b>				
Patients taking EIAEDs	10	3.0 (1.0-5.9)	7.7 (5.7-11.4)	3.62 (2.44-5.28)
Patients taking AEDs with no known effect on drug-metabolizing enzymes	7	5.2 (2.9-6.1)	19.0 (12.9-27.1)	1.2 (0.75-2.42)
Patients taking VPA only	8	2.9 (1.0-6.0)	44.9 (29.5-52.5)	0.47 (0.23-0.77)
<b>Ages 5-11 years</b>				
Patients taking EIAEDs	7	1.6 (1.0-3.0)	7.0 (3.8-9.8)	2.54 (1.35-5.58)
Patients taking EIAEDs plus VPA	8	3.3 (1.0-6.4)	19.1 (7.0-31.2)	0.89 (0.39-1.93)
Patients taking VPA only*	3	4.5 (3.0-6.0)	65.8 (50.7-73.7)	0.24 (0.21-0.26)
<b>Ages 13-18 years</b>				
Patients taking EIAEDs	11	†	†	1.3
Patients taking EIAEDs plus VPA	8	†	†	0.5
Patients taking VPA only	4	†	†	0.3

188 \*Two subjects were included in the calculation for mean t<sub>max</sub>.

189 † Parameter not estimated.

190

191 **Elderly:** In a single-dose study (150 mg of LAMICTAL), the pharmacokinetics of lamotrigine in  
192 12 elderly volunteers between the ages of 65 and 76 years (mean creatinine clearance = 61 mL/min,  
193 range = 33 to 108) were similar to those of young, healthy volunteers in other studies.

194 **Gender:** The clearance of lamotrigine is not affected by gender.

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

197

198 **CLINICAL STUDIES:** The results of controlled clinical trials established the efficacy of LAMICTAL as  
199 monotherapy in adults with partial onset seizures already receiving treatment with a single enzyme  
200 inducing anti-epileptic drug (EIAED), as adjunctive therapy in adults with partial seizures, and as  
201 adjunctive therapy in the generalized seizures of Lennox-Gastaut syndrome in pediatric and adult  
202 patients.

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203 **Monotherapy With LAMICTAL in adults with partial seizures already receiving treatment with a**  
204 **single enzyme inducing anti-epileptic drug (EIAED):** The effectiveness of monotherapy with  
205 LAMICTAL was established in a multicenter, double-blind clinical trial enrolling 156 adult outpatients  
206 with partial seizures. The patients experienced at least four simple partial, complex partial, and/or  
207 secondarily generalized seizures during each of two consecutive 4-week periods while receiving  
208 carbamazepine or phenytoin monotherapy during baseline. LAMICTAL (target dose of 500 mg/day)  
209 or VPA (1000 mg/day) was added to either carbamazepine or phenytoin monotherapy over a 4-week  
210 period. Patients were then converted to monotherapy with LAMICTAL or VPA during the next  
211 4 weeks, then continued on monotherapy for an additional 12-week period.

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

219 The percentage of patients who met escape criteria was 42% (32/76) in the LAMICTAL group and  
220 69% (55/80) in the VPA group. The difference in the percentage of patients meeting escape criteria  
221 was statistically significant ( $P = 0.0012$ ) in favor of LAMICTAL. No differences in efficacy based on  
222 age, sex, or race were detected.

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

227 **Adjunctive Therapy With LAMICTAL in Adults:** The effectiveness of LAMICTAL as adjunctive  
228 therapy (added to other AEDs) was established in three multicenter, placebo-controlled, double-blind  
229 clinical trials in 355 adults with refractory partial seizures. The patients had a history of at least 4  
230 partial seizures per month in spite of receiving one or more AEDs at therapeutic concentrations and,  
231 in 2 of the studies, were observed on their established AED regimen during baselines that varied  
232 between 8 to 12 weeks. In the third, patients were not observed in a prospective baseline. In patients  
233 continuing to have at least 4 seizures per month during the baseline, LAMICTAL or placebo was then  
234 added to the existing therapy. In all three studies, change from baseline in seizure frequency was the  
235 primary measure of effectiveness. The results given below are for all partial seizures in the  
236 intent-to-treat population (all patients who received at least one dose of treatment) in each study,  
237 unless otherwise indicated. The median seizure frequency at baseline was 3 per week while the  
238 mean at baseline was 6.6 per week for all patients enrolled in efficacy studies.

239 One study (n = 216) was a double-blind, placebo-controlled, parallel trial consisting of a 24-week  
240 treatment period. Patients could not be on more than two other anticonvulsants and VPA was not  
241 allowed. Patients were randomized to receive placebo, a target dose of 300 mg/day of LAMICTAL, or  
242 a target dose of 500 mg/day of LAMICTAL. The median reductions in the frequency of all partial

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243 seizures relative to baseline were 8% in patients receiving placebo, 20% in patients receiving  
244 300 mg/day of LAMICTAL, and 36% in patients receiving 500 mg/day of LAMICTAL. The seizure  
245 frequency reduction was statistically significant in the 500-mg/day group compared to the placebo  
246 group, but not in the 300-mg/day group.

247 A second study (n = 98) was a double-blind, placebo-controlled, randomized, crossover trial  
248 consisting of two 14-week treatment periods (the last 2 weeks of which consisted of dose tapering)  
249 separated by a 4-week washout period. Patients could not be on more than two other anticonvulsants  
250 and VPA was not allowed. The target dose of LAMICTAL was 400 mg/day. When the first 12 weeks  
251 of the treatment periods were analyzed, the median change in seizure frequency was a 25%  
252 reduction on LAMICTAL compared to placebo ( $P < 0.001$ ).

253 The third study (n = 41) was a double-blind, placebo-controlled, crossover trial consisting of two  
254 12-week treatment periods separated by a 4-week washout period. Patients could not be on more  
255 than two other anticonvulsants. Thirteen patients were on concomitant VPA; these patients received  
256 150 mg/day of LAMICTAL. The 28 other patients had a target dose of 300 mg/day of LAMICTAL. The  
257 median change in seizure frequency was a 26% reduction on LAMICTAL compared to placebo  
258 ( $P < 0.01$ ).

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

261 **Adjunctive Therapy With LAMICTAL in Pediatric and Adult Patients With Lennox-Gastaut**

262 **Syndrome:** The effectiveness of LAMICTAL as adjunctive therapy in patients with Lennox-Gastaut  
263 syndrome was established in a multicenter, double-blind, placebo-controlled trial in 169 patients aged  
264 3 to 25 years (n = 79 on LAMICTAL, n = 90 on placebo). Following a 4-week single-blind, placebo  
265 phase, patients were randomized to 16 weeks of treatment with LAMICTAL or placebo added to their  
266 current AED regimen of up to three drugs. Patients were dosed on a fixed-dose regimen based on  
267 body weight and VPA use. Target doses were designed to approximate 5 mg/kg per day for patients  
268 taking VPA (maximum dose, 200 mg/day) and 15 mg/kg per day for patients not taking VPA  
269 (maximum dose, 400 mg/day). The primary efficacy endpoint was median reduction from baseline in  
270 major motor seizures (atonic, tonic, major myoclonic, and tonic-clonic seizures). For the  
271 intent-to-treat population, the median reduction of major motor seizures was 32% in patients treated  
272 with LAMICTAL and 9% on placebo, a difference that was statistically significant ( $P < 0.05$ ). Drop  
273 attacks were significantly reduced by LAMICTAL (34%) compared to placebo (9%), as were  
274 tonic-clonic seizures (36% reduction versus 10% increase for LAMICTAL and placebo, respectively).

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276 **INDICATIONS AND USAGE:**

277 **Adjunctive Use:** LAMICTAL is indicated as adjunctive therapy in adults with partial seizures and as  
278 adjunctive therapy in the generalized seizures of Lennox-Gastaut syndrome in pediatric and adult  
279 patients.

280 **Monotherapy Use:** LAMICTAL is indicated for conversion to monotherapy in adults with partial  
281 seizures who are receiving treatment with a single enzyme inducing anti-epileptic drug (EIAED).

282 Safety and effectiveness of LAMICTAL have not been established 1) as initial monotherapy, 2) for

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283 conversion to monotherapy from non-enzyme-inducing AEDs (e.g., valproate), or 3) for simultaneous  
284 conversion to monotherapy from two or more concomitant AEDs (see DOSAGE AND  
285 ADMINISTRATION).

286

287 Safety and effectiveness in patients below the age of 16 other than those with Lennox-Gastaut  
288 syndrome have not been established (see BOX WARNING).

289

290 **CONTRAINDICATIONS:** LAMICTAL is contraindicated in patients who have demonstrated  
291 hypersensitivity to the drug or its ingredients.

292

293 **WARNINGS: SEE BOX WARNING REGARDING THE RISK OF SERIOUS RASHES REQUIRING**  
294 **HOSPITALIZATION AND DISCONTINUATION OF LAMICTAL.**

295 **ALTHOUGH BENIGN RASHES ALSO OCCUR WITH LAMICTAL, IT IS NOT POSSIBLE TO**  
296 **PREDICT RELIABLY WHICH RASHES WILL PROVE TO BE SERIOUS OR LIFE THREATENING.**  
297 **ACCORDINGLY, LAMICTAL SHOULD ORDINARILY BE DISCONTINUED AT THE FIRST SIGN**  
298 **OF RASH, UNLESS THE RASH IS CLEARLY NOT DRUG RELATED. DISCONTINUATION OF**  
299 **TREATMENT MAY NOT PREVENT A RASH FROM BECOMING LIFE THREATENING OR**  
300 **PERMANENTLY DISABLING OR DISFIGURING.**

301 **Serious Rash: Pediatric Population:** The incidence of serious rash associated with hospitalization  
302 and discontinuation of LAMICTAL in a prospectively followed cohort of pediatric patients was  
303 approximately 1.1% (14/1233). When these 14 cases were reviewed by 3 expert dermatologists,  
304 there was considerable disagreement as to their proper classification. To illustrate, one dermatologist  
305 considered none of the cases to be Stevens-Johnson syndrome; another assigned 7 of the 14 to this  
306 diagnosis. There were no deaths or permanent sequelae in these patients. Additionally, there have  
307 been rare cases of toxic epidermal necrolysis with and without permanent sequelae and/or death in  
308 US and foreign postmarketing experience. It bears emphasis, accordingly, that LAMICTAL is only  
309 approved for use in those patients below the age of 16 who have seizures associated with the  
310 Lennox-Gastaut syndrome (see INDICATIONS).

311 Because foreign postmarketing reports suggested that the rate of serious rash was greater with  
312 concomitant VPA use and because metabolism of LAMICTAL is inhibited by VPA, resulting in  
313 increased LAMICTAL plasma levels, the drug development database was examined for concomitant  
314 VPA use. In pediatric patients who used VPA concomitantly, 1.1% (5/443) experienced a serious  
315 rash compared to 1% (6/628) patients not taking VPA. Although the numbers are small, 1.7% (5/294)  
316 patients taking either VPA alone or VPA + non-EIAEDs experienced a serious rash compared to 0%  
317 (0/149) patients taking VPA + EIAEDs.

318 **Adult Population:** Serious rash associated with hospitalization and discontinuation of LAMICTAL  
319 occurred in 0.3% (11/3348) of patients who received LAMICTAL in premarketing clinical trials. No  
320 fatalities occurred among these individuals. However, in worldwide postmarketing experience, rare  
321 cases of rash-related death have been reported, but their numbers are too few to permit a precise  
322 estimate of the rate.

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

326 There is evidence that the inclusion of VPA in a multidrug regimen increases the risk of serious,  
327 potentially life-threatening rash in adults. Specifically, of 584 patients administered LAMICTAL with  
328 VPA in clinical trials, 6 (1%) were hospitalized in association with rash; in contrast, 4 (0.16%) of 2398  
329 clinical trial patients and volunteers administered LAMICTAL in the absence of VPA were  
330 hospitalized.

331 Other examples of serious and potentially life-threatening rash that did not lead to hospitalization  
332 also occurred in premarketing development. Among these, one case was reported to be  
333 Stevens-Johnson–like.

334 **Hypersensitivity Reactions:** Hypersensitivity reactions, some fatal or life threatening, have also  
335 occurred. Some of these reactions have included clinical features of multiorgan dysfunction such as  
336 hepatic abnormalities and evidence of disseminated intravascular coagulation. It is important to note  
337 that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even  
338 though a rash is not evident. If such signs or symptoms are present, the patient should be evaluated  
339 immediately. LAMICTAL should be discontinued if an alternative etiology for the signs or symptoms  
340 cannot be established.

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

345 **Acute Multiorgan Failure:** Fatalities associated with multiorgan failure and various degrees of  
346 hepatic failure have been reported in 2/3796 adult patients and 3/1136 pediatric patients who  
347 received LAMICTAL during premarketing clinical trials. Rare fatalities from multiorgan failure have  
348 also been reported in compassionate plea and postmarketing use. All of these cases occurred in  
349 association with other serious medical events (e.g., status epilepticus, overwhelming sepsis), making  
350 it impossible to identify the initiating cause.

351 Additionally, three patients (a 45-year-old woman, a 3.5-year-old boy, and an 11-year-old girl)  
352 developed multiorgan dysfunction and disseminated intravascular coagulation 9 to 14 days after  
353 LAMICTAL was added to their AED regimens. Rash and elevated transaminases were also present  
354 in all patients and rhabdomyolysis was noted in two patients. Both pediatric patients were receiving  
355 concomitant therapy with VPA, while the adult patient was being treated with carbamazepine and  
356 clonazepam. All patients subsequently recovered with supportive care after treatment with  
357 LAMICTAL was discontinued.

358 **Pure Red Cell Aplasia (PRCA):** A case of PRCA was reported in a 32-year-old male with a history  
359 of  $\beta$ -thalassemia. The patient had a microcytic anemia (hemoglobin 11 g/dL) that was stable while the  
360 patient received carbamazepine but became more severe in the 3 months after LAMICTAL was  
361 added. A bone marrow aspirate revealed markedly decreased erythropoiesis but normal  
362 granulopoiesis and thrombopoiesis. Erythropoiesis resumed after discontinuation of LAMICTAL and

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363 transfusions of packed red cells. Although PRCA is known to occur in patients with  
364 hemoglobinopathies, it is not known if  $\beta$ -thalassemia is a specific risk factor for the development of  
365 PRCA.

366 **Withdrawal Seizures:** As a rule, AEDs should not be abruptly discontinued because of the possibility  
367 of increasing seizure frequency. Unless safety concerns require a more rapid withdrawal, the dose of  
368 LAMICTAL should be tapered over a period of at least 2 weeks (see DOSAGE AND  
369 ADMINISTRATION).

370 **Special Dosing Considerations for Pediatric Patients:** The lowest available strength of LAMICTAL  
371 Chewable Dispersible Tablets is 5 mg, and only whole tablets should be administered. Since the  
372 dosing of LAMICTAL in pediatric patients is based on body weight and the lowest tablet strength is  
373 5 mg, some low-weight pediatric patients should not receive LAMICTAL. Specifically, pediatric  
374 patients who weigh less than 17 kg (37 lb) should not receive LAMICTAL because therapy cannot be  
375 initiated using the dosing guidelines and the currently available tablet strengths (see DOSAGE AND  
376 ADMINISTRATION).

377

378 **PRECAUTIONS:**

379 **Dermatological Events (see BOX WARNING, WARNINGS):** Serious rashes associated with  
380 hospitalization and discontinuation of LAMICTAL have been reported. Rare deaths have been  
381 reported, but their numbers are too few to permit a precise estimate of the rate. There are  
382 suggestions, yet to be proven, that the risk of rash may also be increased by 1) coadministration of  
383 LAMICTAL with VPA, 2) exceeding the recommended initial dose of LAMICTAL, or 3) exceeding the  
384 recommended dose escalation for LAMICTAL. However, cases have been reported in the absence of  
385 these factors.

386 In clinical trials, approximately 10% of all patients exposed to LAMICTAL developed a rash.  
387 Rashes associated with LAMICTAL do not appear to have unique identifying features. Typically, rash  
388 occurs in the first 2 to 8 weeks following treatment initiation. However, isolated cases have been  
389 reported after prolonged treatment (e.g., 6 months). Accordingly, duration of therapy cannot be relied  
390 upon as a means to predict the potential risk heralded by the first appearance of a rash.

391 Although most rashes resolved even with continuation of treatment with LAMICTAL, it is not  
392 possible to predict reliably which rashes will prove to be serious or life threatening. **ACCORDINGLY,**  
393 **LAMICTAL SHOULD ORDINARILY BE DISCONTINUED AT THE FIRST SIGN OF RASH,**  
394 **UNLESS THE RASH IS CLEARLY NOT DRUG RELATED. DISCONTINUATION OF TREATMENT**  
395 **MAY NOT PREVENT A RASH FROM BECOMING LIFE THREATENING OR PERMANENTLY**  
396 **DISABLING OR DISFIGURING.**

397 **Sudden Unexplained Death in Epilepsy (SUDEP):** During the premarketing development of  
398 LAMICTAL, 20 sudden and unexplained deaths were recorded among a cohort of 4700 patients with  
399 epilepsy (5747 patient-years of exposure).

400 Some of these could represent seizure-related deaths in which the seizure was not observed, e.g.,  
401 at night. This represents an incidence of 0.0035 deaths per patient-year. Although this rate exceeds  
402 that expected in a healthy population matched for age and sex, it is within the range of estimates for

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403 the incidence of sudden unexplained deaths in patients with epilepsy not receiving LAMICTAL  
404 (ranging from 0.0005 for the general population of patients with epilepsy, to 0.004 for a recently  
405 studied clinical trial population similar to that in the clinical development program for LAMICTAL, to  
406 0.005 for patients with refractory epilepsy). Consequently, whether these figures are reassuring or  
407 suggest concern depends on the comparability of the populations reported upon to the cohort  
408 receiving LAMICTAL and the accuracy of the estimates provided. Probably most reassuring is the  
409 similarity of estimated SUDEP rates in patients receiving LAMICTAL and those receiving another  
410 antiepileptic drug that underwent clinical testing in a similar population at about the same time.

411 Importantly, that drug is chemically unrelated to LAMICTAL. This evidence suggests, although it  
412 certainly does not prove, that the high SUDEP rates reflect population rates, not a drug effect.

413 **Status Epilepticus:** Valid estimates of the incidence of treatment emergent status epilepticus among  
414 patients treated with LAMICTAL are difficult to obtain because reporters participating in clinical trials  
415 did not all employ identical rules for identifying cases. At a minimum, 7 of 2343 adult patients had  
416 episodes that could unequivocally be described as status. In addition, a number of reports of variably  
417 defined episodes of seizure exacerbation (e.g., seizure clusters, seizure flurries, etc.) were made.

418 **Addition of LAMICTAL to a Multidrug Regimen That Includes VPA (Dosage Reduction):**

419 Because VPA reduces the clearance of lamotrigine, the dosage of lamotrigine in the presence of VPA  
420 is less than half of that required in its absence (see DOSAGE AND ADMINISTRATION).

421 **Use in Patients With Concomitant Illness:** Clinical experience with LAMICTAL in patients with  
422 concomitant illness is limited. Caution is advised when using LAMICTAL in patients with diseases or  
423 conditions that could affect metabolism or elimination of the drug, such as renal, hepatic, or cardiac  
424 functional impairment.

425 Hepatic metabolism to the glucuronide followed by renal excretion is the principal route of  
426 elimination of lamotrigine (see CLINICAL PHARMACOLOGY).

427 A study in individuals with severe chronic renal failure (mean creatinine clearance = 13 mL/min)  
428 not receiving other AEDs indicated that the elimination half-life of unchanged lamotrigine is prolonged  
429 relative to individuals with normal renal function. Until adequate numbers of patients with severe renal  
430 impairment have been evaluated during chronic treatment with LAMICTAL, it should be used with  
431 caution in these patients, generally using a reduced maintenance dose for patients with significant  
432 impairment.

433 Because there is no experience with the use of LAMICTAL in patients with impaired liver function,  
434 the use in such patients may be associated with as yet unrecognized risks.

435 **Binding in the Eye and Other Melanin-Containing Tissues:** Because lamotrigine binds to melanin,  
436 it could accumulate in melanin-rich tissues over time. This raises the possibility that lamotrigine may  
437 cause toxicity in these tissues after extended use. Although ophthalmological testing was performed  
438 in one controlled clinical trial, the testing was inadequate to exclude subtle effects or injury occurring  
439 after long-term exposure. Moreover, the capacity of available tests to detect potentially adverse  
440 consequences, if any, of lamotrigine's binding to melanin is unknown.

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

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443 **Information for Patients:** Prior to initiation of treatment with LAMICTAL, the patient should be  
444 instructed that a rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy)  
445 may herald a serious medical event and that the patient should report any such occurrence to a  
446 physician immediately. In addition, the patient should notify his physician if worsening of seizure  
447 control occurs.

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

453 Patients should be advised to notify their physicians if they become pregnant or intend to become  
454 pregnant during therapy. Patients should be advised to notify their physicians if they intend to  
455 breast-feed or are breast-feeding an infant.

456 Patients should be informed of the availability of a patient information leaflet, and they should be  
457 instructed to read the leaflet prior to taking LAMICTAL. See PATIENT INFORMATION at the end of  
458 this labeling for the text of the leaflet provided for patients.

459 **Laboratory Tests:** The value of monitoring plasma concentrations of LAMICTAL has not been  
460 established. Because of the possible pharmacokinetic interactions between LAMICTAL and other  
461 AEDs being taken concomitantly (see Table 3), monitoring of the plasma levels of LAMICTAL and  
462 concomitant AEDs may be indicated, particularly during dosage adjustments. In general, clinical  
463 judgment should be exercised regarding monitoring of plasma levels of LAMICTAL and other  
464 anti-seizure drugs and whether or not dosage adjustments are necessary.

465 **Drug Interactions: *Antiepileptic Drugs:*** The use of AEDs in combination is complicated by the  
466 potential for pharmacokinetic interactions.

467 The interaction of lamotrigine with phenytoin, carbamazepine, and VPA has been studied. The net  
468 effects of these various AED combinations on individual AED plasma concentrations are summarized  
469 in Table 3.

470

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**Table 3: Summary of AED Interactions With LAMICTAL**

AED	AED Plasma Concentration With Adjunctive LAMICTAL*	Lamotrigine Plasma Concentration With Adjunctive AEDs†
Phenytoin (PHT)	↔	↓
Carbamazepine (CBZ)	↔	↓
CBZ epoxide‡	?	
Valproic acid (VPA)	↓	↑
VPA + PHT and/or CBZ	NE	↔

\* From adjunctive clinical trials and volunteer studies.

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

‡ Not administered, but an active metabolite of carbamazepine.

↔ = No significant effect.

? = Conflicting data.

NE = not evaluated.

***Specific Effects of Lamotrigine on the Pharmacokinetics of Other AED Products:***

***LAMICTAL Added to Phenytoin:*** LAMICTAL has no appreciable effect on steady-state phenytoin plasma concentration.

***LAMICTAL Added to Carbamazepine:*** LAMICTAL has no appreciable effect on steady-state carbamazepine plasma concentration. Limited clinical data suggest there is a higher incidence of dizziness, diplopia, ataxia, and blurred vision in patients receiving carbamazepine with LAMICTAL than in patients receiving other EIAEDs with LAMICTAL (see ADVERSE REACTIONS). The mechanism of this interaction is unclear. The effect of lamotrigine on plasma concentrations of carbamazepine-epoxide is unclear. In a small subset of patients (n = 7) studied in a placebo-controlled trial, lamotrigine had no effect on carbamazepine-epoxide plasma concentrations, but in a small, uncontrolled study (n = 9), carbamazepine-epoxide levels were seen to increase.

***LAMICTAL Added to VPA:*** When LAMICTAL was administered to 18 healthy volunteers receiving VPA in a pharmacokinetic study, the trough steady-state VPA concentrations in plasma decreased by an average of 25% over a 3-week period, and then stabilized. However, adding LAMICTAL to the existing therapy did not cause a change in plasma VPA concentrations in either adult or pediatric patients in controlled clinical trials.

***Specific Effects of Other AED Products on the Pharmacokinetics of Lamotrigine: Phenytoin***

***Added to LAMICTAL:*** The addition of phenytoin decreases lamotrigine steady-state concentrations by approximately 45% to 54% depending upon the total daily dose of phenytoin (i.e., from 100 to 400 mg).

***Carbamazepine Added to LAMICTAL:*** The addition of carbamazepine decreases lamotrigine steady-state concentrations by approximately 40%.

***Phenobarbital or Primidone Added to LAMICTAL:*** The addition of phenobarbital or

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505 primidone decreases lamotrigine steady-state concentrations by approximately 40%.

506 **VPA Added to LAMICTAL:** The addition of VPA increases lamotrigine steady-state  
507 concentrations in normal volunteers by slightly more than twofold.

508 **Interactions With Drug Products Other Than AEDs: Folate Inhibitors:** Lamotrigine is an  
509 inhibitor of dihydrofolate reductase. Prescribers should be aware of this action when prescribing  
510 other medications that inhibit folate metabolism.

511 **Drug/Laboratory Test Interactions:** None known.

512 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** No evidence of carcinogenicity was seen  
513 in one mouse study or two rat studies following oral administration of lamotrigine for up to 2 years at  
514 maximum tolerated doses (30 mg/kg per day for mice and 10 to 15 mg/kg per day for rats, doses that  
515 are equivalent to 90 mg/m<sup>2</sup> and 60 to 90 mg/m<sup>2</sup>, respectively). Steady-state plasma concentrations  
516 ranged from 1 to 4 mcg/mL in the mouse study and 1 to 10 mcg/mL in the rat study. Plasma  
517 concentrations associated with the recommended human doses of 300 to 500 mg/day are generally  
518 in the range of 2 to 5 mcg/mL, but concentrations as high as 19 mcg/mL have been recorded.

519 Lamotrigine was not mutagenic in the presence or absence of metabolic activation when tested in  
520 two gene mutation assays (the Ames test and the in vitro mammalian mouse lymphoma assay). In  
521 two cytogenetic assays (the in vitro human lymphocyte assay and the in vivo rat bone marrow  
522 assay), lamotrigine did not increase the incidence of structural or numerical chromosomal  
523 abnormalities.

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

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

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

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

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

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

558 **Pregnancy Exposure Registry:** To facilitate monitoring fetal outcomes of pregnant women exposed  
559 to lamotrigine, physicians are encouraged to register patients, **before fetal outcome (e.g.,**  
560 **ultrasound, results of amniocentesis, birth, etc.) is known**, in the Antiepileptic Drug Pregnancy  
561 Registry by calling (888) 233-2334 (toll free).

562 **Labor and Delivery:** The effect of LAMICTAL on labor and delivery in humans is unknown.

563 **Use in Nursing Mothers:** Preliminary data indicate that lamotrigine passes into human milk.  
564 Because the effects on the infant exposed to LAMICTAL by this route are unknown, breast-feeding  
565 while taking LAMICTAL is not recommended.

566 **Pediatric Use:** In pediatric patients, LAMICTAL is only indicated as adjunctive therapy for the  
567 generalized seizures of Lennox-Gastaut syndrome. Safety and effectiveness for other uses in  
568 patients below the age of 16 years have not been established (see BOX WARNING).

569 **Geriatric Use:** Because few patients over the age of 65 (approximately 20) were exposed to  
570 LAMICTAL during its premarket evaluation, no specific statements about the safety or effectiveness  
571 of LAMICTAL in this age-group can be made.

572

573 **ADVERSE REACTIONS: SERIOUS RASH REQUIRING HOSPITALIZATION AND**  
574 **DISCONTINUATION OF LAMICTAL, INCLUDING STEVENS-JOHNSON SYNDROME AND TOXIC**  
575 **EPIDERMAL NECROLYSIS, HAVE OCCURRED IN ASSOCIATION WITH THERAPY WITH**  
576 **LAMICTAL. RARE DEATHS HAVE BEEN REPORTED, BUT THEIR NUMBERS ARE TOO FEW**  
577 **TO PERMIT A PRECISE ESTIMATE OF THE RATE (see BOX WARNING).**

578 **Most Common Adverse Events in All Clinical Studies: *Adjunctive Therapy in Adults:*** The most  
579 commonly observed (=5%) adverse experiences seen in association with LAMICTAL during  
580 adjunctive therapy in adults and not seen at an equivalent frequency among placebo-treated patients  
581 were: dizziness, ataxia, somnolence, headache, diplopia, blurred vision, nausea, vomiting, and rash.  
582 Dizziness, diplopia, ataxia, blurred vision, nausea, and vomiting were dose related. Dizziness,  
583 diplopia, ataxia, and blurred vision occurred more commonly in patients receiving carbamazepine  
584 with LAMICTAL than in patients receiving other EIAEDs with LAMICTAL. Clinical data suggest a

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585 higher incidence of rash, including serious rash, in patients receiving concomitant VPA than in  
586 patients not receiving VPA (see WARNINGS).

587 Approximately 11% of the 3378 adult patients who received LAMICTAL as adjunctive therapy in  
588 premarketing clinical trials discontinued treatment because of an adverse experience. The adverse  
589 events most commonly associated with discontinuation were: rash (3.0%), dizziness (2.8%), and  
590 headache (2.5%).

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

593 **Monotherapy in Adults:** The most commonly observed ( $\geq 5\%$ ) adverse experiences seen in  
594 association with the use of LAMICTAL during the monotherapy phase of the controlled trial in adults  
595 not seen at an equivalent rate in the control group were vomiting, coordination abnormality,  
596 dyspepsia, nausea, dizziness, rhinitis, anxiety, insomnia, infection, pain, weight decrease, chest pain,  
597 and dysmenorrhea. The most commonly observed ( $\geq 5\%$ ) adverse experiences associated with the  
598 use of LAMICTAL during the conversion to monotherapy (add-on) period, not seen at an equivalent  
599 frequency among low-dose valproate-treated patients, were dizziness, headache, nausea, asthenia,  
600 coordination abnormality, vomiting, rash, somnolence, diplopia, ataxia, accidental injury, tremor,  
601 blurred vision, insomnia, nystagmus, diarrhea, lymphadenopathy, pruritus, and sinusitis.

602 Approximately 10% of the 420 adult patients who received LAMICTAL as monotherapy in  
603 premarketing clinical trials discontinued treatment because of an adverse experience. The adverse  
604 events most commonly associated with discontinuation were rash (4.5%), headache (3.1%), and  
605 asthenia (2.4%).

606 **Adjunctive Therapy in Pediatric Patients With Lennox-Gastaut Syndrome:** The most  
607 commonly observed ( $\geq 5\%$ ) adverse experiences seen in association with the use of LAMICTAL as  
608 adjunctive treatment in pediatric patients with Lennox-Gastaut syndrome and not seen at an  
609 equivalent rate in the control group were pharyngitis, infection, rash, vomiting, bronchitis, accidental  
610 injury, constipation, and flu syndrome.

611 In 169 patients with Lennox-Gastaut syndrome (26 patients were between the ages of 16 and 25),  
612 3.8% of patients on LAMICTAL and 7.8% of patients on placebo discontinued due to adverse  
613 experiences. The most commonly reported adverse experiences that led to discontinuation were rash  
614 for patients treated with LAMICTAL and deterioration of seizure control for patients treated with  
615 placebo.

616 Approximately 10% of the 1136 pediatric patients who received LAMICTAL as adjunctive therapy  
617 in premarketing clinical trials discontinued treatment because of an adverse experience. The adverse  
618 events most commonly associated with discontinuation were rash (3.9%), reaction aggravated  
619 (1.7%), and ataxia (0.9%).

620 **Incidence in Controlled Clinical Studies:** The prescriber should be aware that the figures in Tables  
621 4, 5, 6, and 7 cannot be used to predict the frequency of adverse experiences in the course of usual  
622 medical practice where patient characteristics and other factors may differ from those prevailing  
623 during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures  
624 obtained from other clinical investigations involving different treatments, uses, or investigators. An

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625 inspection of these frequencies, however, does provide the prescriber with one basis to estimate the  
626 relative contribution of drug and nondrug factors to the adverse event incidences in the population  
627 studied.

628 ***Incidence in Controlled Adjunctive Clinical Studies in Adults:*** Table 4 lists  
629 treatment-emergent signs and symptoms that occurred in at least 2% of adult patients with epilepsy  
630 treated with LAMICTAL in placebo-controlled trials and were numerically more common in the  
631 patients treated with LAMICTAL. In these studies, either LAMICTAL or placebo was added to the  
632 patient's current AED therapy. Adverse events were usually mild to moderate in intensity.

633  
634  
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636  
637  
638

**Table 4: Treatment-Emergent Adverse Event Incidence  
in Placebo-Controlled Adjunctive Trials\*  
(Events in at least 2% of patients treated with LAMICTAL  
and numerically more frequent than in the placebo group.)**

Body System/ Adverse Experience <sup>†</sup>	Percent of Patients Receiving Adjunctive LAMICTAL (n = 711)	Percent of Patients Receiving Adjunctive Placebo (n = 419)
<b>Body as a whole</b>		
Headache	29	19
Flu syndrome	7	6
Fever	6	4
Abdominal pain	5	4
Neck pain	2	1
Reaction aggravated (seizure exacerbation)	2	1
<b>Digestive</b>		
Nausea	19	10
Vomiting	9	4
Diarrhea	6	4
Dyspepsia	5	2
Constipation	4	3
Tooth disorder	3	2
Anorexia	2	1
<b>Musculoskeletal</b>		
Arthralgia	2	0
<b>Nervous</b>		
Dizziness	38	13

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Ataxia	22	6
Somnolence	14	7
Incoordination	6	2
Insomnia	6	2
Tremor	4	1
Depression	4	3
Anxiety	4	3
Convulsion	3	1
Irritability	3	2
Speech disorder	3	0
Concentration disturbance	2	1
Respiratory		
Rhinitis	14	9
Pharyngitis	10	9
Cough increased	8	6
Skin and appendages		
Rash	10	5
Pruritus	3	2
Special senses		
Diplopia	28	7
Blurred vision	16	5
Vision abnormality	3	1
Urogenital		
Female patients only	(n = 365)	(n = 207)
Dysmenorrhea	7	6
Vaginitis	4	1
Amenorrhea	2	1

639 \* Patients in these adjunctive studies were receiving one to three concomitant EIAEDs in addition  
 640 to LAMICTAL or placebo. Patients may have reported multiple adverse experiences during the  
 641 study or at discontinuation; thus, patients may be included in more than one category.

642 † Adverse experiences reported by at least 2% of patients treated with LAMICTAL are included.

643

644 In a randomized, parallel study comparing placebo and 300 and 500 mg/day of LAMICTAL, some  
 645 of the more common drug-related adverse events were dose related (see Table 5).

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**Table 5: Dose-Related Adverse Events From a Randomized, Placebo-Controlled Trial in Adults**

Adverse Experience	Percent of Patients Experiencing Adverse Experiences		
	Placebo (n = 73)	LAMICTAL 300 mg (n = 71)	LAMICTAL 500 mg (n = 72)
Ataxia	10	10	28*†
Blurred vision	10	11	25*†
Diplopia	8	24*	49*†
Dizziness	27	31	54*†
Nausea	11	18	25*
Vomiting	4	11	18*

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\*Significantly greater than placebo group ( $P < 0.05$ ).

†Significantly greater than group receiving LAMICTAL 300 mg ( $P < 0.05$ ).

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Other events that occurred in more than 1% of patients but equally or more frequently in the placebo group included: asthenia, back pain, chest pain, flatulence, menstrual disorder, myalgia, paresthesia, respiratory disorder, and urinary tract infection.

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

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***Incidence in a Controlled Monotherapy Trial in Adults With Partial Seizures:*** Table 6 lists treatment-emergent signs and symptoms that occurred in at least 2% of patients with epilepsy treated with monotherapy with LAMICTAL in a double-blind trial following discontinuation of either concomitant carbamazepine or phenytoin not seen at an equivalent frequency in the control group.

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**Table 6: Treatment-Emergent Adverse Event Incidence in Adults in a Controlled Monotherapy Trial\* (Events in at least 2% of patients treated with LAMICTAL and numerically more frequent than in the valproate [VPA] group.)**

Body System/ Adverse Experience†	Percent of Patients Receiving LAMICTAL Monotherapy‡ (n = 43)	Percent of Patients Receiving Low-Dose VPA§ Monotherapy (n = 44)
-------------------------------------	--	--

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Body as a whole		
Pain	5	0
Infection	5	2
Chest pain	5	2
Asthenia	2	0
Fever	2	0
Digestive		
Vomiting	9	0
Dyspepsia	7	2
Nausea	7	2
Anorexia	2	0
Dry mouth	2	0
Rectal hemorrhage	2	0
Peptic ulcer	2	0
Metabolic and nutritional		
Weight decrease	5	2
Peripheral edema	2	0
Nervous		
Coordination abnormality	7	0
Dizziness	7	0
Anxiety	5	0
Insomnia	5	2
Amnesia	2	0
Ataxia	2	0
Depression	2	0
Hypesthesia	2	0
Libido increase	2	0
Decreased reflexes	2	0
Increased reflexes	2	0
Nystagmus	2	0
Irritability	2	0
Suicidal ideation	2	0
Respiratory		
Rhinitis	7	2
Epistaxis	2	0
Bronchitis	2	0
Dyspnea	2	0
Skin and appendages		
Contact dermatitis	2	0
Dry skin	2	0

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Sweating	2	0
Special senses		
Vision abnormality	2	0
Urogenital (female patients only)	(n = 21)	(n = 28)
Dysmenorrhea	5	0

675 \* Patients in these studies were converted to LAMICTAL or VPA monotherapy from adjunctive therapy  
 676 with carbamazepine or phenytoin. Patients may have reported multiple adverse experiences during the  
 677 study; thus, patients may be included in more than one category.

678 † Adverse experiences reported by at least 2% of patients are included.

679 ‡ Up to 500 mg/day.

680 § 1000 mg/day.

681

682 ***Incidence in a Controlled Adjunctive Trial in Adult and Pediatric Patients With***  
 683 ***Lennox-Gastaut Syndrome:*** Table 7 lists adverse events that occurred in at least 2% of 79 adult  
 684 and pediatric patients who received LAMICTAL up to 15 mg/kg per day or a maximum of 400 mg/kg  
 685 per day. Reported adverse events were classified using COSTART terminology.

686

687 **Table 7: Treatment-Emergent Adverse Event Incidence in Placebo-Controlled**  
 688 **Adjunctive Trial in Adult and Pediatric Patients With Lennox-Gastaut Syndrome**  
 689 **(Events in at least 2% of patients treated with LAMICTAL and numerically more**  
 690 **frequent than in the placebo group.)**  
 691

Body System/ Adverse Experience	Percent of Patients Receiving LAMICTAL (n = 79)	Percent of Patients Receiving Placebo (n = 90)
Body as a whole		
Infection	13	8
Accidental injury	9	7
Flu syndrome	5	0
Asthenia	3	1
Abdominal pain	3	0
Cardiovascular		
Hemorrhage	3	0
Digestive		
Vomiting	9	7
Constipation	5	2
Diarrhea	4	2

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Nausea	4	1
Anorexia	3	1
Nervous system		
Ataxia	4	1
Convulsions	4	1
Tremor	3	0
Respiratory		
Pharyngitis	14	10
Bronchitis	9	7
Pneumonia	3	0
Skin		
Rash	9	7
Eczema	4	0
Urogenital		
Urinary tract infection	3	0
Balanitis	2	0
Penis disorder	2	0

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693 **Other Adverse Events Observed During All Clinical Trials For Adult and Pediatric Patients:**

694 LAMICTAL has been administered to 3923 individuals for whom complete adverse event data was  
695 captured during all clinical trials, only some of which were placebo controlled. During these trials, all  
696 adverse events were recorded by the clinical investigators using terminology of their own choosing.  
697 To provide a meaningful estimate of the proportion of individuals having adverse events, similar types  
698 of events were grouped into a smaller number of standardized categories using modified COSTART  
699 dictionary terminology. The frequencies presented represent the proportion of the 3923 individuals  
700 exposed to LAMICTAL who experienced an event of the type cited on at least one occasion while  
701 receiving LAMICTAL. All reported events are included except those already listed in the previous  
702 table, those too general to be informative, and those not reasonably associated with the use of the  
703 drug.

704 Events are further classified within body system categories and enumerated in order of decreasing  
705 frequency using the following definitions: *frequent* adverse events are defined as those occurring in at  
706 least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; *rare*  
707 adverse events are those occurring in fewer than 1/1000 patients.

708 **Body as a Whole: Frequent:** Pain. **Infrequent:** Accidental injury, allergic reaction, back pain,  
709 chills, face edema, halitosis, infection, and malaise. **Rare:** Abdomen enlarged, abscess,  
710 photosensitivity, and suicide attempt.

711 **Cardiovascular System: Infrequent:** Flushing, hot flashes, migraine, palpitations, postural  
712 hypotension, syncope, tachycardia, and vasodilation. **Rare:** Angina pectoris, atrial fibrillation, deep  
713 thrombophlebitis, hemorrhage, hypertension, and myocardial infarction.

714 **Dermatological: Infrequent:** Acne, alopecia, dry skin, erythema, hirsutism, maculopapular rash,  
715 skin discoloration, Stevens-Johnson syndrome, sweating, urticaria, and vesiculobullous rash. **Rare:**  
716 Angioedema, erythema multiforme, fungal dermatitis, herpes zoster, leukoderma, petechial rash,  
717 pustular rash, and seborrhea.

718 **Digestive System: Infrequent:** Dry mouth, dysphagia, gingivitis, glossitis, gum hyperplasia,  
719 increased appetite, increased salivation, liver function tests abnormal, mouth ulceration, stomatitis,  
720 thirst, and tooth disorder. **Rare:** Eructation, gastritis, gastrointestinal hemorrhage, gum hemorrhage,  
721 hematemesis, hemorrhagic colitis, hepatitis, melena, stomach ulcer, and tongue edema.

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

723 **Hematologic and Lymphatic System: Infrequent:** Anemia, ecchymosis, leukocytosis,  
724 leukopenia, lymphadenopathy, and petechia. **Rare:** Eosinophilia, fibrin decrease, fibrinogen  
725 decrease, iron deficiency anemia, lymphocytosis, macrocytic anemia, and thrombocytopenia.

726 **Metabolic and Nutritional Disorders: Infrequent:** Peripheral edema, weight gain, and weight  
727 loss. **Rare:** Alcohol intolerance, alkaline phosphatase increase, bilirubinemia, general edema, and  
728 hyperglycemia.

729 **Musculoskeletal System: Infrequent:** Joint disorder, myasthenia, and twitching. **Rare:** Arthritis,  
730 bursitis, leg cramps, pathological fracture, and tendinous contracture.

731 **Nervous System: Frequent:** Amnesia, confusion, hostility, memory decrease, nervousness,  
732 nystagmus, thinking abnormality, and vertigo. **Infrequent:** Abnormal dreams, abnormal gait,

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733 agitation, akathisia, apathy, aphasia, CNS depression, depersonalization, dysarthria, dyskinesia,  
734 dysphoria, emotional lability, euphoria, faintness, grand mal convulsions, hallucinations, hyperkinesia,  
735 hypertonia, hypesthesia, libido increased, mind racing, muscle spasm, myoclonus, panic attack,  
736 paranoid reaction, personality disorder, psychosis, sleep disorder, and stupor. **Rare:** Cerebrovascular  
737 accident, cerebellar syndrome, cerebral sinus thrombosis, choreoathetosis, CNS stimulation,  
738 delirium, delusions, dystonia, hemiplegia, hyperalgesia, hyperesthesia, hypoesthesia, hypokinesia,  
739 hypomania, hypotonia, libido decreased, manic depression reaction, movement disorder, neuralgia,  
740 neurosis, paralysis, and suicidal ideation.

741 **Respiratory System: Infrequent:** Dyspnea, epistaxis, and hyperventilation. **Rare:**  
742 Bronchospasm, hiccup, and sinusitis.

743 **Special Senses: Infrequent:** Abnormality of accommodation, conjunctivitis, ear pain, oscillopsia,  
744 photophobia, taste perversion, and tinnitus. **Rare:** Deafness, dry eyes, lacrimation disorder,  
745 parosmia, ptosis, strabismus, taste loss, and uveitis.

746 **Urogenital System: Infrequent:** Female lactation, hematuria, polyuria, urinary frequency, urinary  
747 incontinence, urinary retention, and vaginal moniliasis. **Rare:** Abnormal ejaculation, acute kidney  
748 failure, breast abscess, breast neoplasm, breast pain, creatinine increase, cystitis, dysuria,  
749 epididymitis, impotence, kidney failure, kidney pain, menorrhagia, and urine abnormality.

750 **Postmarketing and Other Experience:** In addition to the adverse experiences reported during  
751 clinical testing of LAMICTAL, the following adverse experiences have been reported in patients  
752 receiving marketed LAMICTAL in other countries and from worldwide noncontrolled investigational  
753 use. These adverse experiences have not been listed above, and data are insufficient to support an  
754 estimate of their incidence or to establish causation. The listing is alphabetized: Aplastic anemia,  
755 apnea, disseminated intravascular coagulation, esophagitis, hemolytic anemia, hypersensitivity  
756 reaction, multiorgan failure, neutropenia, pancreatitis, pancytopenia, and progressive  
757 immunosuppression.

758

759 **DRUG ABUSE AND DEPENDENCE:** The abuse and dependence potential of LAMICTAL have not  
760 been evaluated in human studies.

761

762 **OVERDOSAGE:**

763 **Human Overdose Experience:** Experience with single or daily doses  $\geq 700$  mg is limited. During the  
764 clinical development of LAMICTAL, the highest known overdoses were in two women who each  
765 ingested doses  $\geq 4000$  mg. The plasma concentration of lamotrigine in one woman was 52 mcg/mL  
766 4 hours after the ingestion (a value more than 10 times greater than that seen in clinical trials). She  
767 became comatose and remained comatose for 8 to 12 hours; no electrocardiographic abnormalities  
768 were detected. The other patient had dizziness, headache, and somnolence. Both women recovered  
769 without sequelae.

770 Among patients  $\leq 16$  years of age, the two highest known single doses of LAMICTAL have been  
771 3000 mg by a 14-year-old female and approximately 1000 mg by a 4-year-old male. The 14-year-old  
772 female was taking LAMICTAL; after the dose, she lost consciousness and was admitted to the

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773 hospital for supportive therapy, where she recovered fully (time to recovery not reported). The  
774 4-year-old male was drowsy and agitated when found, and progressed to coma. He was given  
775 supportive therapy, and his condition improved rapidly with full recovery in 3 days.

776 **Management of Overdose:** There are no specific antidotes for LAMICTAL. Following a suspected  
777 overdose, hospitalization of the patient is advised. General supportive care is indicated, including  
778 frequent monitoring of vital signs and close observation of the patient. If indicated, emesis should be  
779 induced or gastric lavage should be performed; usual precautions should be taken to protect the  
780 airway. It should be kept in mind that lamotrigine is rapidly absorbed (see CLINICAL  
781 PHARMACOLOGY). It is uncertain whether hemodialysis is an effective means of removing  
782 lamotrigine from the blood. In six renal failure patients, about 20% of the amount of lamotrigine in the  
783 body was removed by hemodialysis during a 4-hour session. A Poison Control Center should be  
784 contacted for information on the management of overdosage of LAMICTAL.

785

786 **DOSAGE AND ADMINISTRATION:**

787 **Adjunctive Use:** LAMICTAL is indicated as adjunctive therapy in adults with partial seizures and as  
788 adjunctive therapy in the generalized seizures of Lennox-Gastaut syndrome in pediatric and adult  
789 patients.

790 **Monotherapy Use:** LAMICTAL is indicated for conversion to monotherapy in adults with partial  
791 seizures who are receiving treatment with a single enzyme inducing anti-epileptic drug (EIAED, e.g.,  
792 carbamazepine, phenytoin, phenobarbital, etc.).

793 **Safety and effectiveness of LAMICTAL have not been established 1) as initial monotherapy,**  
794 **2) for conversion to monotherapy from non-enzyme-inducing AEDs (e.g., valproate), or 3) for**  
795 **simultaneous conversion to monotherapy from two or more concomitant AEDs.**

796

797

798 **Safety and effectiveness in pediatric patients below the age of 16 years other than those**  
799 **with Lennox-Gastaut syndrome have not been established (see BOX WARNING).**

800

801 **General Dosing Considerations:** The risk of nonserious rash is increased when the recommended  
802 initial dose and/or the rate of dose escalation of LAMICTAL is exceeded. There are suggestions, yet  
803 to be proven, that the risk of severe, potentially life-threatening rash may be increased by  
804 1) coadministration of LAMICTAL with valproic acid (VPA), 2) exceeding the recommended initial  
805 dose of LAMICTAL, or 3) exceeding the recommended dose escalation for LAMICTAL. However,  
806 cases have been reported in the absence of these factors (see BOX WARNING). Therefore, it is  
807 important that the dosing recommendations be followed closely.

808 **Adjunctive Therapy With LAMICTAL:** This section provides specific dosing recommendations for  
809 patients 2 to 12 years of age and patients greater than 12 years of age. Within each of these  
810 age-groups, specific dosing recommendations are provided depending upon whether or not the  
811 patient is receiving VPA (Tables 8 and 9 for patients 2 to 12 years of age, Tables 10 and 11 for  
812 patients greater than 12 years of age). In addition, the section provides a discussion of dosing for

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813 those patients receiving concomitant AEDs that have not been systematically evaluated in  
814 combination with LAMICTAL.

815 For dosing guidelines for LAMICTAL below, enzyme-inducing antiepileptic drugs (EIAEDs) include  
816 phenytoin, carbamazepine, phenobarbital, and primidone.

817 **Patients 2 to 12 Years of Age:** Recommended dosing guidelines for LAMICTAL added to an  
818 antiepileptic drug (AED) regimen containing VPA are summarized in Table 8. Recommended dosing  
819 guidelines for LAMICTAL added to EIAEDs are summarized in Table 9. Note that the starting doses  
820 and dose escalations listed below are different than those used in clinical trials; however, the  
821 maintenance doses are the same as in clinical trials. Smaller starting doses and slower dose  
822 escalations than those used in clinical trials are recommended because of the suggestions that the  
823 risk of rash may be decreased by smaller starting doses and slower dose escalations. Therefore,  
824 maintenance doses will take longer to reach in clinical practice than in clinical trials. It may take  
825 several weeks to months to achieve an individualized maintenance dose. It is likely that patients aged  
826 2 to 6 years will require a maintenance dose at the higher end of the maintenance dose range.

827 **The smallest available strength of LAMICTAL Chewable Dispersible Tablets is 5 mg, and**  
828 **only whole tablets should be administered. If the calculated dose cannot be achieved using**  
829 **whole tablets, the dose should be rounded down to the nearest whole tablet.**

830 **Pediatric patients who weigh less than 17 kg (37 lb) should not receive LAMICTAL because**  
831 **therapy cannot be initiated using the dosing guidelines (see Table 8 and Table 9) and the**  
832 **currently available tablet strengths (see WARNINGS).**

833

834

**Table 8: LAMICTAL Added to an AED Regimen Containing VPA  
in Patients 2 to 12 Years of Age**

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Weeks 1 and 2	0.15 mg/kg/day in one or two divided doses, rounded down to the nearest 5 mg. If the initial calculated daily dose of LAMICTAL is 2.5 to 5 mg, then 5 mg of LAMICTAL should be taken on alternate days for the first 2 weeks
Weeks 3 and 4	0.3 mg/kg/day in one or two divided doses, rounded down to the nearest 5 mg.
Usual maintenance dose: 1 to 5 mg/kg/day (maximum 200 mg/day in one or two divided doses). To achieve the usual maintenance dose, subsequent doses should be increased every 1 to 2 weeks as follows: calculate 0.3 mg/kg/day, round this amount down to the nearest 5 mg, and add this amount to the previously administered daily dose.	

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839

**Table 9: LAMICTAL Added to EIAEDs (Without VPA) in Patients 2 to 12 Years of Age**

Weeks 1 and 2	0.6 mg/kg/day in two divided doses, rounded down to the nearest 5 mg.
Weeks 3 and 4	1.2 mg/kg/day in two divided doses, rounded down to the nearest 5 mg.
Usual maintenance dose: 5 to 15 mg/kg/day (maximum 400 mg/day in two divided doses). To achieve the usual maintenance dose, subsequent doses should be increased every 1 to 2 weeks as follows: calculate 1.2 mg/kg/day, round this amount down to the nearest 5 mg, and add this amount to the previously administered daily dose.	

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**Patients Over 12 Years of Age:** Recommended dosing guidelines for LAMICTAL added to VPA are summarized in Table 10. Recommended dosing guidelines for LAMICTAL added to EIAEDs are summarized in Table 11.

**Table 10: LAMICTAL Added to an AED Regimen Containing VPA in Patients Over 12 Years of Age**

Weeks 1 and 2	25 mg every <i>other</i> day
Weeks 3 and 4	25 mg every day
Usual maintenance dose: 100 to 400 mg/day (1 or 2 divided doses). To achieve maintenance, doses may be increased by 25 to 50 mg/day every 1 to 2 weeks. The usual maintenance dose in patients adding LAMICTAL to VPA alone ranges from 100 to 200 mg/day.	

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**Table 11: LAMICTAL Added to EIAEDs (Without VPA) in Patients Over 12 Years of Age**

Weeks 1 and 2	50 mg/day
Weeks 3 and 4	100 mg/day in two divided doses
Usual maintenance dose: 300 to 500 mg/day (in two divided doses). To achieve maintenance, doses may be increased by 100 mg/day every 1 to 2 weeks.	

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**Conversion From a Single EIAED to Monotherapy with LAMICTAL in Patients ≥16 Years of**

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

The conversion regimen involves two steps. In the first, LAMICTAL is titrated to the targeted dose while maintaining the dose of the EIAED at a fixed level; in the second step, the EIAED is gradually withdrawn over a period of 4 weeks.

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

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862 LAMICTAL should be added to an EIAED to achieve a dose of 500 mg/day according to the  
863 guidelines in Table 11 above. The regimen for the withdrawal of the concomitant EIAED is based on  
864 experience gained in the controlled monotherapy clinical trial. In that trial, the concomitant EIAED  
865 was withdrawn by 20% decrements each week over a 4-week period.

866 Because of an increased risk of rash, the recommended initial dose and subsequent dose  
867 escalations of LAMICTAL should not be exceeded (see BOX WARNING).

868 **Usual Maintenance Dose:** The usual maintenance doses identified in the tables above are derived  
869 from dosing regimens employed in the placebo-controlled adjunctive studies in which the efficacy of  
870 LAMICTAL was established. In patients receiving multidrug regimens employing EIAEDs **without**  
871 **VPA**, maintenance doses of adjunctive LAMICTAL as high as 700 mg/day have been used. In  
872 patients receiving **VPA alone**, maintenance doses of adjunctive LAMICTAL as high as 200 mg/day  
873 have been used. The advantage of using doses above those recommended in the tables above has  
874 not been established in controlled trials.

875 **LAMICTAL Added to AEDs Other Than EIAEDs and VPA:** The effect of AEDs other than EIAEDs  
876 and VPA on the metabolism of LAMICTAL cannot be predicted. Therefore, no specific dosing  
877 guidelines can be provided in that situation. Conservative starting doses and dose escalations (as  
878 with concomitant VPA) would be prudent; maintenance dosing would be expected to fall between the  
879 maintenance dose with VPA and the maintenance dose without VPA, but with an EIAED.

880 **Patients With Renal Functional Impairment:** Initial doses of LAMICTAL should be based on  
881 patients' AED regimen (see above); reduced maintenance doses may be effective for patients with  
882 significant renal functional impairment (see CLINICAL PHARMACOLOGY). Few patients with severe  
883 renal impairment have been evaluated during chronic treatment with LAMICTAL. Because there is  
884 inadequate experience in this population, LAMICTAL should be used with caution in these patients.

885 **Discontinuation Strategy:** For patients receiving LAMICTAL in combination with other AEDs, a  
886 reevaluation of all AEDs in the regimen should be considered if a change in seizure control or an  
887 appearance or worsening of adverse experiences is observed.

888 If a decision is made to discontinue therapy with LAMICTAL, a step-wise reduction of dose over at  
889 least 2 weeks (approximately 50% per week) is recommended unless safety concerns require a more  
890 rapid withdrawal (see PRECAUTIONS).

891 *Discontinuing an EIAED should prolong the half-life of lamotrigine; discontinuing VPA should*  
892 *shorten the half-life of lamotrigine.*

893 **Target Plasma Levels:** A therapeutic plasma concentration range has not been established for  
894 lamotrigine. Dosing of LAMICTAL should be based on therapeutic response.

895 **Administration of LAMICTAL Chewable Dispersible Tablets:** LAMICTAL Chewable Dispersible  
896 Tablets may be swallowed whole, chewed, or dispersed in water or diluted fruit juice. If the tablets are  
897 chewed, consume a small amount of water or diluted fruit juice to aid in swallowing.

898 To disperse LAMICTAL Chewable Dispersible Tablets, add the tablets to a small amount of liquid  
899 (1 teaspoon, or enough to cover the medication). Approximately 1 minute later, when the tablets are  
900 completely dispersed, swirl the solution and consume the entire quantity immediately. *No attempt*  
901 *should be made to administer partial quantities of the dispersed tablets.*

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902

903 **HOW SUPPLIED:** LAMICTAL Tablets, 25 mg, white, scored, shield-shaped tablets engraved with  
904 "LAMICTAL" and "25", bottles of 25 (NDC 0173-0633-25) and 100 (NDC 0173-0633-02).

905 **Store at 15° to 25°C (59° to 77°F) in a dry place.**

906 LAMICTAL Tablets, 100 mg, peach, scored, shield-shaped tablets engraved with "LAMICTAL" and  
907 "100", bottle of 100 (NDC 0173-0642-55).

908 LAMICTAL Tablets, 150 mg, cream, scored, shield-shaped tablets engraved with "LAMICTAL"  
909 and "150", bottle of 60 (NDC 0173-0643-60).

910 LAMICTAL Tablets, 200 mg, blue, scored, shield-shaped tablets engraved with "LAMICTAL" and  
911 "200", bottle of 60 (NDC 0173-0644-60).

912 **Store at 15° to 25°C (59° to 77°F) in a dry place and protect from light.**

913 LAMICTAL Chewable Dispersible Tablets, 5 mg, white, caplet-shaped tablets engraved with  
914 "GX CL2", bottle of 100 (NDC 0173-0526-00).

915 LAMICTAL Chewable Dispersible Tablets, 25 mg, white, super elliptical-shaped tablets engraved  
916 with "GX CL5", bottle of 100 (NDC 0173-0527-00).

917 **Store at controlled room temperature, 20° to 25°C (68° to 77°F) (see USP) in a dry place.**

918

919 **PATIENT INFORMATION:** The following wording is contained in a separate leaflet provided for  
920 patients.

921

**Information for the Patient**





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 <b>25 mg, white</b>	 <b>100 mg, peach</b>	 <b>150 mg, cream</b>	 <b>200 mg, blue</b>
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**LAMICTAL® (lamotrigine) Chewable Dispersible Tablets**

 <b>5 mg, white</b>	 <b>25 mg, white</b>
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930 Please read this leaflet carefully before you take LAMICTAL and read the leaflet provided with any  
931 refill, in case any information has changed. This leaflet provides a summary of the information about  
932 your medicine. Please do not throw away this leaflet until you have finished your medicine. This  
933 leaflet does not contain all the information about LAMICTAL and is not meant to take the place of  
934 talking with your doctor. If you have any questions about LAMICTAL, ask your doctor or pharmacist.

935 **Information About Your Medicine:**

936 The name of your medicine is LAMICTAL (lamotrigine). The decision to use LAMICTAL is one that  
937 you and your doctor should make together.

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

938 **1. The Purpose of Your Medicine:**

939 Lamotrigine is intended to be used either alone or in combination with other medicines to treat  
940 seizures in people age 16 years or older and/or only those patients below the age of 16 years who  
941 have seizures associated with the Lennox-Gastaut syndrome. When taking lamotrigine, it is important  
942 to follow your doctor's instructions.

943 **2. Who Should Not Take LAMICTAL:**

944 You should not take LAMICTAL if you had an allergic reaction to it in the past.

945 **3. Side Effects to Watch for:**

- 946 • Most people who take LAMICTAL tolerate it well. The most common side effects with LAMICTAL  
947 are dizziness, headache, blurred or double vision, lack of coordination, sleepiness, nausea,  
948 vomiting, and rash.
- 949 • Although most patients who develop rash while receiving LAMICTAL have mild to moderate  
950 symptoms, some individuals may develop a serious skin reaction that requires hospitalization.  
951 Rarely, deaths have been reported. These serious skin reactions are most likely to happen within  
952 the first 8 weeks of treatment with LAMICTAL. Serious skin reactions occur more often in children  
953 than in adults.
- 954 • Rashes may be more likely to occur if you: 1) take LAMICTAL in combination with valproic acid  
955 (DEPAKENE® or DEPAKOTE®), 2) take a higher starting dose of LAMICTAL than your doctor  
956 prescribed, or 3) increase your dose of LAMICTAL faster than prescribed.
- 957 • It is not possible to predict whether a mild rash will develop into a more serious reaction.

958 **Therefore, if you experience a skin rash, hives, fever, swollen lymph glands, painful sores**  
959 **in the mouth or around the eyes, or swelling of lips or tongue, tell a doctor immediately,**  
960 **since these symptoms may be the first signs of a serious reaction. A doctor should**  
961 **evaluate your condition and decide if you should continue taking LAMICTAL.**

962 **4. The Use of LAMICTAL During Pregnancy and Breast-feeding:**

963 The effects of LAMICTAL during pregnancy are not known at this time. If you are pregnant or are  
964 planning to become pregnant, talk to your doctor. Some LAMICTAL passes into breast milk and the  
965 effects of this on infants are unknown. Therefore, if you are breast-feeding, you should discuss this  
966 with your doctor to determine if you should continue to take LAMICTAL.

967 **5. How to Use LAMICTAL:**

- 968 • It is important to take LAMICTAL exactly as instructed by your doctor. The dose of LAMICTAL  
969 must be increased slowly. It may take several weeks or months before your final dosage can be  
970 determined by your doctor, based on your response.
- 971 • Do not increase your dose of LAMICTAL or take more frequent doses than those indicated by  
972 your doctor.
- 973 • If you miss a dose of LAMICTAL, do not double your next dose.
- 974 • Do NOT stop taking LAMICTAL or any of your other seizure medicines unless instructed by your  
975 doctor.
- 976 • Use caution before driving a car or operating complex, hazardous machinery until you know if  
977 LAMICTAL affects your ability to perform these tasks.

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

- 978 • Tell your doctor if your seizures get worse or if you have any new types of seizures.  
979 • Always tell your doctor and pharmacist if you are taking or plan to take any other prescription or  
980 over-the-counter medicines.

981 **6. How to Take LAMICTAL:**

982 LAMICTAL Tablets should be swallowed whole. Chewing the tablets may leave a bitter taste.  
983 LAMICTAL Chewable Dispersible Tablets may be swallowed whole, chewed, or mixed in water or  
984 diluted fruit juice. If the tablets are chewed, consume a small amount of water or diluted fruit juice to  
985 aid in swallowing.

986 To disperse LAMICTAL Chewable Dispersible Tablets, add the tablets to a small amount of liquid  
987 (1 teaspoon, or enough to cover the medication) in a glass or spoon. Approximately 1 minute later,  
988 when the tablets are completely dispersed, mix the solution and take the entire amount immediately.

989 **7. Storing Your Medicine:**

990 Store LAMICTAL at room temperature away from heat and light. Always keep your medicines out  
991 of the reach of children.

992 This medicine was prescribed for your use only to treat seizures. Do not give the drug to others.

993 If your doctor decides to stop your treatment, do not keep any leftover medicine unless your  
994 doctor tells you to. Throw away your medicine as instructed.

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997 **GlaxoWellcome**

998 Glaxo Wellcome Inc.

999 Research Triangle Park, NC 27709

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1003 US Patent No. 4,602,017

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1007 October 1998

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**PHARMACIST—DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT**

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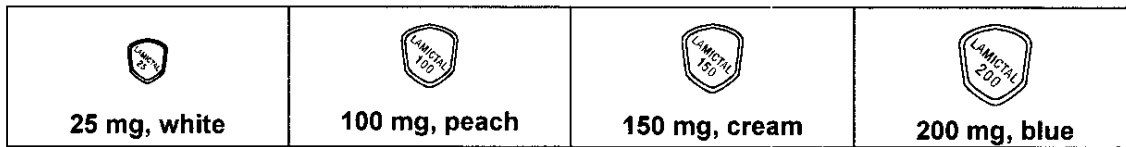
**Information for the Patient**

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

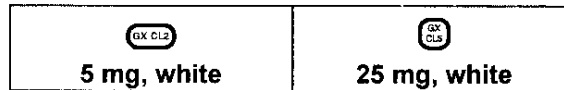
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**LAMICTAL® (lamotrigine) Tablets**



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



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**LAMICTAL® (lamotrigine) Tablets**  
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1096 November 1998

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