

[17-JAN-2003]

1 **LAMICTAL[®]**
2 **(lamotrigine)**
3 **Tablets**

PRODUCT INFORMATION

4
5 **LAMICTAL[®]**
6 **(lamotrigine)**
7 **Chewable Dispersible Tablets**
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9
10 **SERIOUS RASHES REQUIRING HOSPITALIZATION AND DISCONTINUATION**
11 **OF TREATMENT HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE**
12 **OF LAMICTAL. THE INCIDENCE OF THESE RASHES, WHICH HAVE**
13 **INCLUDED STEVENS-JOHNSON SYNDROME, IS APPROXIMATELY**
14 **0.8% (8 PER 1000). IN PEDIATRIC PATIENTS (AGE <16 YEARS) RECEIVING**
15 **LAMICTAL AS ADJUNCTIVE THERAPY AND 0.3% (3 PER 1000) IN ADULTS. IN**
16 **A PROSPECTIVELY FOLLOWED COHORT OF 1,983 PEDIATRIC PATIENTS**
17 **TAKING ADJUNCTIVE LAMICTAL, THERE WAS 1 RASH-RELATED DEATH.**
18 **IN WORLDWIDE POSTMARKETING EXPERIENCE, RARE CASES OF TOXIC**
19 **EPIDERMAL NECROLYSIS AND/OR RASH-RELATED DEATH HAVE BEEN**
20 **REPORTED IN ADULT AND PEDIATRIC PATIENTS, BUT THEIR NUMBERS**
21 **ARE TOO FEW TO PERMIT A PRECISE ESTIMATE OF THE RATE.**

22 **BECAUSE THE RATE OF SERIOUS RASH IS GREATER IN PEDIATRIC**
23 **PATIENTS THAN IN ADULTS, IT BEARS EMPHASIS THAT LAMICTAL IS**
24 **APPROVED ONLY FOR USE IN PEDIATRIC PATIENTS BELOW THE AGE OF**
25 **16 YEARS WHO HAVE SEIZURES ASSOCIATED WITH THE**
26 **LENNOX-GASTAUT SYNDROME OR IN PATIENTS WITH PARTIAL SEIZURES**
27 **(SEE INDICATIONS).**

28 **OTHER THAN AGE, THERE ARE AS YET NO FACTORS IDENTIFIED THAT**
29 **ARE KNOWN TO PREDICT THE RISK OF OCCURRENCE OR THE SEVERITY**
30 **OF RASH ASSOCIATED WITH LAMICTAL. THERE ARE SUGGESTIONS, YET**
31 **TO BE PROVEN, THAT THE RISK OF RASH MAY ALSO BE INCREASED BY 1)**
32 **COADMINISTRATION OF LAMICTAL WITH VALPROIC ACID (VPA), 2)**
33 **EXCEEDING THE RECOMMENDED INITIAL DOSE OF LAMICTAL, OR 3)**
34 **EXCEEDING THE RECOMMENDED DOSE ESCALATION FOR LAMICTAL.**
35 **HOWEVER, CASES HAVE BEEN REPORTED IN THE ABSENCE OF THESE**
36 **FACTORS.**

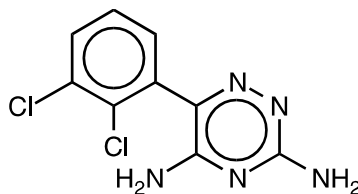
37 **NEARLY ALL CASES OF LIFE-THREATENING RASHES ASSOCIATED**
38 **WITH LAMICTAL HAVE OCCURRED WITHIN 2 TO 8 WEEKS OF**
39 **TREATMENT INITIATION. HOWEVER, ISOLATED CASES HAVE BEEN**

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40 **REPORTED AFTER PROLONGED TREATMENT (e.g., 6 MONTHS).**
41 **ACCORDINGLY, DURATION OF THERAPY CANNOT BE RELIED UPON AS A**
42 **MEANS TO PREDICT THE POTENTIAL RISK HERALDED BY THE FIRST**
43 **APPEARANCE OF A RASH.**

44 **ALTHOUGH BENIGN RASHES ALSO OCCUR WITH LAMICTAL, IT IS NOT**
45 **POSSIBLE TO PREDICT RELIABLY WHICH RASHES WILL PROVE TO BE**
46 **SERIOUS OR LIFE THREATENING. ACCORDINGLY, LAMICTAL SHOULD**
47 **ORDINARILY BE DISCONTINUED AT THE FIRST SIGN OF RASH, UNLESS**
48 **THE RASH IS CLEARLY NOT DRUG RELATED. DISCONTINUATION OF**
49 **TREATMENT MAY NOT PREVENT A RASH FROM BECOMING LIFE**
50 **THREATENING OR PERMANENTLY DISABLING OR DISFIGURING.**

51
52 **DESCRIPTION:** LAMICTAL (lamotrigine), an antiepileptic drug (AED) of the
53 phenyltriazine class, is chemically unrelated to existing antiepileptic drugs. Its chemical
54 name is 3,5-diamino-6-(2,3-dichlorophenyl)-*as*-triazine, its molecular formula is C₉H₇N₅Cl₂,
55 and its molecular weight is 256.09. Lamotrigine is a white to pale cream-colored powder
56 and has a pK_a of 5.7. Lamotrigine is very slightly soluble in water (0.17 mg/mL at 25°C)
57 and slightly soluble in 0.1 M HCl (4.1 mg/mL at 25°C). The structural formula is:



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60
61 LAMICTAL Tablets are supplied for oral administration as 25-mg (white), 100-mg
62 (peach), 150-mg (cream), and 200-mg (blue) tablets. Each tablet contains the labeled
63 amount of lamotrigine and the following inactive ingredients: lactose; magnesium stearate;
64 microcrystalline cellulose; povidone; sodium starch glycolate; FD&C Yellow No. 6 Lake
65 (100-mg tablet only); ferric oxide, yellow (150-mg tablet only); and FD&C Blue No. 2 Lake
66 (200-mg tablet only).

67 LAMICTAL Chewable Dispersible Tablets are supplied for oral administration. The
68 tablets contain 2 mg (white), 5 mg (white), or 25 mg (white) of lamotrigine and the
69 following inactive ingredients: blackcurrant flavor, calcium carbonate, low-substituted
70 hydroxypropylcellulose, magnesium aluminum silicate, magnesium stearate, povidone,
71 saccharin sodium, and sodium starch glycolate.

72
73 **CLINICAL PHARMACOLOGY:**

74 **Mechanism of Action:** The precise mechanism(s) by which lamotrigine exerts its
75 anticonvulsant action are unknown. In animal models designed to detect anticonvulsant

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76 activity, lamotrigine was effective in preventing seizure spread in the maximum
77 electroshock (MES) and pentylenetetrazol (scMet) tests, and prevented seizures in the
78 visually and electrically evoked after-discharge (EEAD) tests for antiepileptic activity. The
79 relevance of these models to human epilepsy, however, is not known.

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

85 **Pharmacological Properties:** Although the relevance for human use is unknown, the
86 following data characterize the performance of LAMICTAL in receptor binding assays.
87 Lamotrigine had a weak inhibitory effect on the serotonin 5-HT₃ receptor (IC₅₀ = 18 μM). It
88 does not exhibit high affinity binding (IC₅₀>100 μM) to the following neurotransmitter
89 receptors: adenosine A₁ and A₂; adrenergic α₁, α₂, and β; dopamine D₁ and D₂; γ-
90 aminobutyric acid (GABA) A and B; histamine H₁; kappa opioid; muscarinic acetylcholine;
91 and serotonin 5-HT₂. Studies have failed to detect an effect of lamotrigine on
92 dihydropyridine-sensitive calcium channels. It had weak effects at sigma opioid receptors
93 (IC₅₀ = 145 μM). Lamotrigine did not inhibit the uptake of norepinephrine, dopamine,
94 serotonin, or aspartic acid (IC₅₀>100 μM).

95 ***Effect of Lamotrigine on N-Methyl d-Aspartate (NMDA)-Mediated Activity:***

96 Lamotrigine did not inhibit NMDA-induced depolarizations in rat cortical slices or
97 NMDA-induced cyclic GMP formation in immature rat cerebellum, nor did lamotrigine
98 displace compounds that are either competitive or noncompetitive ligands at this glutamate
99 receptor complex (CNQX, CGS, TCHP). The IC₅₀ for lamotrigine effects on
100 NMDA-induced currents (in the presence of 3 μM of glycine) in cultured hippocampal
101 neurons exceeded 100 μM.

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

111 ***Accumulation in Kidneys:*** Lamotrigine was found to accumulate in the kidney of the
112 male rat, causing chronic progressive nephrosis, necrosis, and mineralization. These
113 findings are attributed to α-2 microglobulin, a species- and sex-specific protein that has not
114 been detected in humans or other animal species.

115 ***Melanin Binding:*** Lamotrigine binds to melanin-containing tissues, e.g., in the eye and

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116 pigmented skin. It has been found in the uveal tract up to 52 weeks after a single dose in
117 rodents.

118 **Cardiovascular:** In dogs, lamotrigine is extensively metabolized to a 2-N-methyl
119 metabolite. This metabolite causes dose-dependent prolongations of the PR interval,
120 widening of the QRS complex, and, at higher doses, complete AV conduction block. Similar
121 cardiovascular effects are not anticipated in humans because only trace amounts of the
122 2-N-methyl metabolite (<0.6% of lamotrigine dose) have been found in human urine (see
123 Drug Disposition below). However, it is conceivable that plasma concentrations of this
124 metabolite could be increased in patients with a reduced capacity to glucuronidate
125 lamotrigine (e.g., in patients with liver disease).

126 **Pharmacokinetics and Drug Metabolism:** The pharmacokinetics of lamotrigine have been
127 studied in patients with epilepsy, healthy young and elderly volunteers, and volunteers with
128 chronic renal failure. Lamotrigine pharmacokinetic parameters for adult and pediatric
129 patients and healthy normal 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) [†] :				
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)

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

138 [†]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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141 Lamotrigine is eliminated more rapidly in patients who have been taking hepatic EIAEDs,
142 including carbamazepine, phenytoin, phenobarbital, and primidone. Most clinical
143 experience is derived from this population.

144 **VPA, however, actually decreases the apparent clearance of lamotrigine (i.e., more**
145 **than doubles the elimination half-life of lamotrigine).** Accordingly, if lamotrigine is to be
146 administered to a patient receiving VPA, lamotrigine must be given at a reduced dosage, less
147 than half the dose used in patients not receiving VPA (see DOSAGE AND
148 ADMINISTRATION and PRECAUTIONS: Drug Interactions).

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

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

160 **Protein Binding:** Data from in vitro studies indicate that lamotrigine is approximately
161 55% bound to human plasma proteins at plasma lamotrigine concentrations from 1 to
162 10 mcg/mL (10 mcg/mL is four to six times the trough plasma concentration observed in the
163 controlled efficacy trials). Because lamotrigine is not highly bound to plasma proteins,
164 clinically significant interactions with other drugs through competition for protein binding
165 sites are unlikely. The binding of lamotrigine to plasma proteins did not change in the
166 presence of therapeutic concentrations of phenytoin, phenobarbital, or VPA. Lamotrigine
167 did not displace other AEDs (carbamazepine, phenytoin, phenobarbital) from protein
168 binding sites.

169 **Drug Disposition:** Lamotrigine is metabolized predominantly by glucuronic acid
170 conjugation; the major metabolite is an inactive 2-N-glucuronide conjugate. After oral
171 administration of 240 mg of ¹⁴C-lamotrigine (15 µCi) to six healthy volunteers, 94% was
172 recovered in the urine and 2% was recovered in the feces. The radioactivity in the urine
173 consisted of unchanged lamotrigine (10%), the 2-N-glucuronide (76%), a 5-N-glucuronide
174 (10%), a 2-N-methyl metabolite (0.14%), and other unidentified minor metabolites (4%).

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

177 Following multiple administrations (150 mg twice daily) to normal volunteers taking no
178 other medications, lamotrigine induced its own metabolism, resulting in a 25% decrease in
179 T_{1/2} and a 37% increase in Cl/F at steady state compared to values obtained in the same
180 volunteers following a single dose. Evidence gathered from other sources suggests that

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181 self-induction by LAMICTAL may not occur when LAMICTAL is given as adjunctive
182 therapy in patients receiving EIAEDs.

183 **Dose Proportionality:** In healthy volunteers not receiving any other medications and
184 given single doses, the plasma concentrations of lamotrigine increased in direct proportion
185 to the dose administered over the range of 50 to 400 mg. In two small studies (n = 7 and 8)
186 of patients with epilepsy who were maintained on other AEDs, there also was a linear
187 relationship between dose and lamotrigine plasma concentrations at steady state following
188 doses of 50 to 350 mg twice daily.

189 **Elimination:** (see Table 1)

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

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

200 **Age: Pediatric Patients:** The pharmacokinetics of LAMICTAL following a single
201 2 mg/kg dose were evaluated in 2 studies of pediatric patients (n = 29 for patients aged
202 10 months to 5.9 years and n = 26 for patients aged 5 to 11 years). Forty-three patients
203 received concomitant therapy with other AEDs and 12 patients received LAMICTAL as
204 monotherapy. Lamotrigine pharmacokinetic parameters for pediatric patients are
205 summarized in Table 2.

206 Population pharmacokinetic analyses involving patients aged 2 to 18 years demonstrated
207 that lamotrigine clearance was influenced predominantly by total body weight and
208 concurrent AED therapy. The oral clearance of lamotrigine was higher, on a body weight
209 basis, in pediatric patients than in adults. Weight-normalized lamotrigine clearance was
210 higher in those subjects weighing less than 30 kg, compared with those weighing greater
211 than 30 kg. Accordingly, patients weighing less than 30 kg may need an increase of as much
212 as 50% in maintenance doses, based on clinical response, as compared with subjects
213 weighing more than 30 kg being administered the same AEDs. (see DOSAGE AND
214 ADMINISTRATION). These analyses also revealed that, after accounting for body weight,
215 lamotrigine clearance was not significantly influenced by age. Thus, the same weight-
216 adjusted doses should be administered to children irrespective of differences in age.
217 Concomitant AEDs which influence lamotrigine clearance in adults were found to have
218 similar effects in children.

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

Pediatric Study Population	Number of Subjects	t _{max} (h)	t _{1/2} (h)	Cl/F (mL/min/kg)
Ages 10 months-5.3 years				
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)
Ages 5-11 years				
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)
Ages 13-18 years				
Patients taking EIAEDs	11	†	†	1.3
Patients taking EIAEDs plus VPA	8	†	†	0.5
Patients taking VPA only	4	†	†	0.3

221 *Two subjects were included in the calculation for mean t_{max}.

222 † Parameter not estimated.

223

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

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

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

231

232 **CLINICAL STUDIES:** The results of controlled clinical trials established the efficacy of
233 LAMICTAL as monotherapy in adults with partial onset seizures already receiving
234 treatment with a single enzyme-inducing antiepileptic drug (EIAED), as adjunctive therapy
235 in adults and pediatric patients age 2 to 16 with partial seizures, and as adjunctive therapy in
236 the generalized seizures of Lennox-Gastaut syndrome in pediatric and adult patients.

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237 **Monotherapy With LAMICTAL in Adults With Partial Seizures Already Receiving**
238 **Treatment With a Single EIAED:** The effectiveness of monotherapy with LAMICTAL
239 was established in a multicenter, double-blind clinical trial enrolling 156 adult outpatients
240 with partial seizures. The patients experienced at least four simple partial, complex partial,
241 and/or secondarily generalized seizures during each of two consecutive 4-week periods
242 while receiving carbamazepine or phenytoin monotherapy during baseline. LAMICTAL
243 (target dose of 500 mg/day) or VPA (1000 mg/day) was added to either carbamazepine or
244 phenytoin monotherapy over a 4-week period. Patients were then converted to monotherapy
245 with LAMICTAL or VPA during the next 4 weeks, then continued on monotherapy for an
246 additional 12-week period.

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

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

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

262 **Adjunctive Therapy With LAMICTAL in Adults With Partial Seizures:** The
263 effectiveness of LAMICTAL as adjunctive therapy (added to other AEDs) was established
264 in three multicenter, placebo-controlled, double-blind clinical trials in 355 adults with
265 refractory partial seizures. The patients had a history of at least 4 partial seizures per month
266 in spite of receiving one or more AEDs at therapeutic concentrations and, in 2 of the studies,
267 were observed on their established AED regimen during baselines that varied between 8 to
268 12 weeks. In the third, patients were not observed in a prospective baseline. In patients
269 continuing to have at least 4 seizures per month during the baseline, LAMICTAL or placebo
270 was then added to the existing therapy. In all three studies, change from baseline in seizure
271 frequency was the primary measure of effectiveness. The results given below are for all
272 partial seizures in the intent-to-treat population (all patients who received at least one dose
273 of treatment) in each study, unless otherwise indicated. The median seizure frequency at
274 baseline was 3 per week while the mean at baseline was 6.6 per week for all patients
275 enrolled in efficacy studies.

276 One study (n = 216) was a double-blind, placebo-controlled, parallel trial consisting of a

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277 24-week treatment period. Patients could not be on more than two other anticonvulsants and
278 VPA was not allowed. Patients were randomized to receive placebo, a target dose of
279 300 mg/day of LAMICTAL, or a target dose of 500 mg/day of LAMICTAL. The median
280 reductions in the frequency of all partial seizures relative to baseline were 8% in patients
281 receiving placebo, 20% in patients receiving 300 mg/day of LAMICTAL, and 36% in
282 patients receiving 500 mg/day of LAMICTAL. The seizure frequency reduction was
283 statistically significant in the 500-mg/day group compared to the placebo group, but not in
284 the 300-mg/day group.

285 A second study (n = 98) was a double-blind, placebo-controlled, randomized, crossover
286 trial consisting of two 14-week treatment periods (the last 2 weeks of which consisted of
287 dose tapering) separated by a 4-week washout period. Patients could not be on more than
288 two other anticonvulsants and VPA was not allowed. The target dose of LAMICTAL was
289 400 mg/day. When the first 12 weeks of the treatment periods were analyzed, the median
290 change in seizure frequency was a 25% reduction on LAMICTAL compared to placebo
291 ($P < 0.001$).

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

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

300 **Adjunctive Therapy With LAMICTAL in Pediatric Patients with Partial Seizures:** The
301 effectiveness of LAMICTAL as adjunctive therapy in pediatric patients with partial seizures
302 was established in a multicenter, double-blind, placebo-controlled trial in 199 patients aged
303 2 to 16 years (n = 98 on LAMICTAL, n = 101 on placebo). Following an 8-week baseline
304 phase, patients were randomized to 18 weeks of treatment with LAMICTAL or placebo
305 added to their current AED regimen of up to two drugs. Patients were dosed based on body
306 weight and VPA use. Target doses were designed to approximate 5 mg/kg per day for
307 patients taking VPA (maximum dose, 250 mg/day) and 15 mg/kg per day for the patients not
308 taking VPA (maximum dose, 750 mg per day). The primary efficacy endpoint was
309 percentage change from baseline in all partial seizures. For the intent-to-treat population, the
310 median reduction of all partial seizures was 36% in patients treated with LAMICTAL and
311 7% on placebo, a difference that was statistically significant ($P < 0.01$).

312 **Adjunctive Therapy With LAMICTAL in Pediatric and Adult Patients With**
313 **Lennox-Gastaut Syndrome:** The effectiveness of LAMICTAL as adjunctive therapy in
314 patients with Lennox-Gastaut syndrome was established in a multicenter, double-blind,
315 placebo-controlled trial in 169 patients aged 3 to 25 years (n = 79 on LAMICTAL, n = 90 on
316 placebo). Following a 4-week single-blind, placebo phase, patients were randomized to 16

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317 weeks of treatment with LAMICTAL or placebo added to their current AED regimen of up
318 to three drugs. Patients were dosed on a fixed-dose regimen based on body weight and VPA
319 use. Target doses were designed to approximate 5 mg/kg per day for patients taking VPA
320 (maximum dose, 200 mg/day) and 15 mg/kg per day for patients not taking VPA (maximum
321 dose, 400 mg/day). The primary efficacy endpoint was percentage change from baseline in
322 major motor seizures (atonic, tonic, major myoclonic, and tonic-clonic seizures). For the
323 intent-to-treat population, the median reduction of major motor seizures was 32% in patients
324 treated with LAMICTAL and 9% on placebo, a difference that was statistically significant
325 ($P<0.05$). Drop attacks were significantly reduced by LAMICTAL (34%) compared to
326 placebo (9%), as were tonic-clonic seizures (36% reduction versus 10% increase for
327 LAMICTAL and placebo, respectively).

328

329 **INDICATIONS AND USAGE:**

330 **Adjunctive Use:** LAMICTAL is indicated as adjunctive therapy for partial seizures in
331 adults and pediatric patients (≥ 2 years of age).

332 LAMICTAL is also indicated as adjunctive therapy for the generalized seizures of
333 Lennox-Gastaut syndrome in adult and pediatric patients (≥ 2 years of age).

334 **Monotherapy Use:** LAMICTAL is indicated for conversion to monotherapy in adults with
335 partial seizures who are receiving treatment with a single EIAED.

336 Safety and effectiveness of LAMICTAL have not been established 1) as initial
337 monotherapy, 2) for conversion to monotherapy from non-enzyme-inducing AEDs (e.g.,
338 valproate), or 3) for simultaneous conversion to monotherapy from two or more concomitant
339 AEDs (see DOSAGE AND ADMINISTRATION).

340 Safety and effectiveness in patients below the age of 16 other than those with partial
341 seizures and the generalized seizures of Lennox-Gastaut syndrome have not been
342 established (see BOX WARNING).

343

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

346

347 **WARNINGS: SEE BOX WARNING REGARDING THE RISK OF SERIOUS**
348 **RASHES REQUIRING HOSPITALIZATION AND DISCONTINUATION OF**
349 **LAMICTAL.**

350 **ALTHOUGH BENIGN RASHES ALSO OCCUR WITH LAMICTAL, IT IS NOT**
351 **POSSIBLE TO PREDICT RELIABLY WHICH RASHES WILL PROVE TO BE**
352 **SERIOUS OR LIFE THREATENING. ACCORDINGLY, LAMICTAL SHOULD**
353 **ORDINARILY BE DISCONTINUED AT THE FIRST SIGN OF RASH, UNLESS**
354 **THE RASH IS CLEARLY NOT DRUG RELATED. DISCONTINUATION OF**
355 **TREATMENT MAY NOT PREVENT A RASH FROM BECOMING LIFE**
356 **THREATENING OR PERMANENTLY DISABLING OR DISFIGURING.**

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357 **Serious Rash: Pediatric Population:** The incidence of serious rash associated with
358 hospitalization and discontinuation of LAMICTAL in a prospectively followed cohort of
359 pediatric patients receiving adjunctive therapy was approximately 0.8% (16 of 1,983). When
360 14 of these cases were reviewed by 3 expert dermatologists, there was considerable
361 disagreement as to their proper classification. To illustrate, one dermatologist considered
362 none of the cases to be Stevens-Johnson syndrome; another assigned 7 of the 14 to this
363 diagnosis. There was one rash related death in this 1,983 patient cohort.
364 Additionally, there have been rare cases of toxic epidermal necrolysis with and without
365 permanent sequelae and/or death in US and foreign postmarketing experience. It bears
366 emphasis, accordingly, that LAMICTAL is only approved for use in those patients below
367 the age of 16 who have partial seizures or generalized seizures associated with the
368 Lennox-Gastaut syndrome (see INDICATIONS).

369 There is evidence that the inclusion of VPA in a multidrug regimen increases the risk of
370 serious, potentially life-threatening rash in pediatric patients. In pediatric patients who used
371 VPA concomitantly, 1.2% (6 of 482) experienced a serious rash compared to 0.6% (6 of
372 952) patients not taking VPA.

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

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

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

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

390 **Hypersensitivity Reactions:** Hypersensitivity reactions, some fatal or life threatening, have
391 also occurred. Some of these reactions have included clinical features of multiorgan
392 failure/dysfunction, including hepatic abnormalities and evidence of disseminated
393 intravascular coagulation. It is important to note that early manifestations of hypersensitivity
394 (e.g., fever, lymphadenopathy) may be present even though a rash is not evident. If such
395 signs or symptoms are present, the patient should be evaluated immediately. LAMICTAL
396 should be discontinued if an alternative etiology for the signs or symptoms cannot be

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397 established.

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

402 **Acute Multiorgan Failure:** Multiorgan failure, which in some cases has been fatal or
403 irreversible, has been observed in patients receiving LAMICTAL. Fatalities associated with
404 multiorgan failure and various degrees of hepatic failure have been reported in 2 of 3796
405 adult patients and 4 of 2435 pediatric patients who received LAMICTAL in clinical trials.
406 Rare fatalities from multiorgan failure have also been reported in compassionate plea and
407 postmarketing use. The majority of these deaths occurred in association with other serious
408 medical events, including status epilepticus and overwhelming sepsis, and hantavirus
409 making it difficult to identify the initial cause.

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

417 **Blood Dyscrasias:** There have been reports of blood dyscrasias that may or may not be
418 associated with the hypersensitivity syndrome. These have included neutropenia,
419 leukopenia, anemia, thrombocytopenia, pancytopenia and , rarely, aplastic anemia and pure
420 red cell aplasia.

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

425

426 **PRECAUTIONS:**

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

434 In clinical trials, approximately 10% of all patients exposed to LAMICTAL developed a
435 rash. Rashes associated with LAMICTAL do not appear to have unique identifying features.
436 Typically, rash occurs in the first 2 to 8 weeks following treatment initiation. However,

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437 isolated cases have been reported after prolonged treatment (e.g., 6 months). Accordingly,
438 duration of therapy cannot be relied upon as a means to predict the potential risk heralded by
439 the first appearance of a rash.

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

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

450 Some of these could represent seizure-related deaths in which the seizure was not
451 observed, e.g., at night. This represents an incidence of 0.0035 deaths per patient-year.
452 Although this rate exceeds that expected in a healthy population matched for age and sex, it
453 is within the range of estimates for the incidence of sudden unexplained deaths in patients
454 with epilepsy not receiving LAMICTAL (ranging from 0.0005 for the general population of
455 patients with epilepsy, to 0.004 for a recently studied clinical trial population similar to that
456 in the clinical development program for LAMICTAL, to 0.005 for patients with refractory
457 epilepsy). Consequently, whether these figures are reassuring or suggest concern depends on
458 the comparability of the populations reported upon to the cohort receiving LAMICTAL and
459 the accuracy of the estimates provided. Probably most reassuring is the similarity of
460 estimated SUDEP rates in patients receiving LAMICTAL and those receiving another
461 antiepileptic drug that underwent clinical testing in a similar population at about the same
462 time. Importantly, that drug is chemically unrelated to LAMICTAL. This evidence suggests,
463 although it certainly does not prove, that the high SUDEP rates reflect population rates, not
464 a drug effect.

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

471 **Addition of LAMICTAL to a Multidrug Regimen That Includes VPA (Dosage**
472 **Reduction):** Because VPA reduces the clearance of lamotrigine, the dosage of lamotrigine
473 in the presence of VPA is less than half of that required in its absence (see DOSAGE AND
474 ADMINISTRATION).

475 **Use in Patients With Concomitant Illness:** Clinical experience with LAMICTAL in
476 patients with concomitant illness is limited. Caution is advised when using LAMICTAL in

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477 patients with diseases or conditions that could affect metabolism or elimination of the drug,
478 such as renal, hepatic, or cardiac functional impairment.

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

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

487 Because there is no experience with the use of LAMICTAL in patients with impaired
488 liver function, the use in such patients may be associated with as yet unrecognized risks
489 **Binding in the Eye and Other Melanin-Containing Tissues:** Because lamotrigine binds to
490 melanin, it could accumulate in melanin-rich tissues over time. This raises the possibility
491 that lamotrigine may cause toxicity in these tissues after extended use. Although
492 ophthalmological testing was performed in one controlled clinical trial, the testing was
493 inadequate to exclude subtle effects or injury occurring after long-term exposure. Moreover,
494 the capacity of available tests to detect potentially adverse consequences, if any, of
495 lamotrigine's binding to melanin is unknown.

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

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

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

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

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

515 **Laboratory Tests:** The value of monitoring plasma concentrations of LAMICTAL has not

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516 been established. Because of the possible pharmacokinetic interactions between
 517 LAMICTAL and other AEDs being taken concomitantly (see Table 3), monitoring of the
 518 plasma levels of LAMICTAL and concomitant AEDs may be indicated, particularly during
 519 dosage adjustments. In general, clinical judgment should be exercised regarding monitoring
 520 of plasma levels of LAMICTAL and other anti-seizure drugs and whether or not dosage
 521 adjustments are necessary.

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

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

527
 528

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	↔

529 * From adjunctive clinical trials and volunteer studies.

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

532 [‡] Not administered, but an active metabolite of carbamazepine.

533 ↔ = No significant effect.

534 ? = Conflicting data.

535 NE = Not evaluated.

536

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

537
 538 **LAMICTAL Added to Phenytoin:** LAMICTAL has no appreciable effect on steady-state
 539 phenytoin plasma concentration.

540 **LAMICTAL Added to Carbamazepine:** LAMICTAL has no appreciable effect on
 541 steady-state carbamazepine plasma concentration. Limited clinical data suggest there is a
 542 higher incidence of dizziness, diplopia, ataxia, and blurred vision in patients receiving
 543 carbamazepine with LAMICTAL than in patients receiving other EIAEDs with LAMICTAL
 544 (see ADVERSE REACTIONS). The mechanism of this interaction is unclear. The effect of
 545 lamotrigine on plasma concentrations of carbamazepine-epoxide is unclear. In a small subset

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546 of patients (n = 7) studied in a placebo-controlled trial, lamotrigine had no effect on
547 carbamazepine-epoxide plasma concentrations, but in a small, uncontrolled study (n = 9),
548 carbamazepine-epoxide levels were seen to increase.

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

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

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

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

560 **Phenobarbital or Primidone Added to LAMICTAL:** The addition of phenobarbital or
561 primidone decreases lamotrigine steady-state concentrations by approximately 40%.

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

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

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

568 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** No evidence of carcinogenicity
569 was seen in one mouse study or two rat studies following oral administration of lamotrigine
570 for up to 2 years at maximum tolerated doses (30 mg/kg per day for mice and 10 to
571 15 mg/kg per day for rats, doses that are equivalent to 90 mg/m² and 60 to 90 mg/m²,
572 respectively). Steady-state plasma concentrations ranged from 1 to 4 mcg/mL in the mouse
573 study and 1 to 10 mcg/mL in the rat study. Plasma concentrations associated with the
574 recommended human doses of 300 to 500 mg/day are generally in the range of 2 to
575 5 mcg/mL, but concentrations as high as 19 mcg/mL have been recorded.

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

581 No evidence of impairment of fertility was detected in rats given oral doses of
582 lamotrigine up to 2.4 times the highest usual human maintenance dose of 8.33 mg/kg per
583 day or 0.4 times the human dose on a mg/m² basis. The effect of lamotrigine on human
584 fertility is unknown.

585 **Pregnancy:** Pregnancy Category C. No evidence of teratogenicity was found in mice, rats,

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586 or rabbits when lamotrigine was orally administered to pregnant animals during the period
587 of organogenesis at doses up to 1.2, 0.5, and 1.1 times, respectively, on a mg/m² basis, the
588 highest usual human maintenance dose (i.e., 500 mg/day). However, maternal toxicity and
589 secondary fetal toxicity producing reduced fetal weight and/or delayed ossification were
590 seen in mice and rats, but not in rabbits at these doses. Teratology studies were also
591 conducted using bolus intravenous administration of the isethionate salt of lamotrigine in
592 rats and rabbits. In rat dams administered an intravenous dose at 0.6 times the highest usual
593 human maintenance dose, the incidence of intrauterine death without signs of teratogenicity
594 was increased.

595 A behavioral teratology study was conducted in rats dosed during the period of
596 organogenesis. At day 21 postpartum, offspring of dams receiving 5 mg/kg per day or higher
597 displayed a significantly longer latent period for open field exploration and a lower
598 frequency of rearing. In a swimming maze test performed on days 39 to 44 postpartum, time
599 to completion was increased in offspring of dams receiving 25 mg/kg per day. These doses
600 represent 0.1 and 0.5 times the clinical dose on a mg/m² basis, respectively.

601 Lamotrigine did not affect fertility, teratogenesis, or postnatal development when rats
602 were dosed prior to and during mating, and throughout gestation and lactation at doses
603 equivalent to 0.4 times the highest usual human maintenance dose on a mg/m² basis.

604 When pregnant rats were orally dosed at 0.1, 0.14, or 0.3 times the highest human
605 maintenance dose (on a mg/m² basis) during the latter part of gestation (days 15 to 20),
606 maternal toxicity and fetal death were seen. In dams, food consumption and weight gain
607 were reduced, and the gestation period was slightly prolonged (22.6 vs. 22.0 days in the
608 control group). Stillborn pups were found in all three drug-treated groups with the highest
609 number in the high-dose group. Postnatal death was also seen, but only in the two highest
610 doses, and occurred between day 1 and 20. Some of these deaths appear to be drug-related
611 and not secondary to the maternal toxicity. A no-observed-effect level (NOEL) could not be
612 determined for this study.

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

619 **Pregnancy Exposure Registry:** To facilitate monitoring fetal outcomes of pregnant women
620 exposed to lamotrigine, physicians are encouraged to register patients, **before fetal outcome**
621 **(e.g., ultrasound, results of amniocentesis, birth, etc.) is known**, and can obtain
622 information by calling the Lamotrigine Pregnancy Registry at (800) 336-2176 (toll-free).
623 Patients can enroll themselves in the North American Antiepileptic Drug Pregnancy
624 Registry by calling (888) 233-2334 (toll free).

625 **Labor and Delivery:** The effect of LAMICTAL on labor and delivery in humans is

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626 unknown.

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

630 **Pediatric Use:** LAMICTAL is indicated as adjunctive therapy for partial seizures in patients
631 above 2 years of age and for the generalized seizures of Lennox-Gastaut syndrome. Safety
632 and effectiveness for other uses in patients below the age of 16 years have not been
633 established. (see BOX WARNING).

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

637

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

644 **Most Common Adverse Events in All Clinical Studies: *Adjunctive Therapy in Adults:***

645 The most commonly observed ($\geq 5\%$) adverse experiences seen in association with
646 LAMICTAL during adjunctive therapy in adults and not seen at an equivalent frequency
647 among placebo-treated patients were: dizziness, ataxia, somnolence, headache, diplopia,
648 blurred vision, nausea, vomiting, and rash. Dizziness, diplopia, ataxia, blurred vision,
649 nausea, and vomiting were dose related. Dizziness, diplopia, ataxia, and blurred vision
650 occurred more commonly in patients receiving carbamazepine with LAMICTAL than in
651 patients receiving other EIAEDs with LAMICTAL. Clinical data suggest a higher incidence
652 of rash, including serious rash, in patients receiving concomitant VPA than in patients not
653 receiving VPA (see WARNINGS).

654 Approximately 11% of the 3378 adult patients who received LAMICTAL as adjunctive
655 therapy in premarketing clinical trials discontinued treatment because of an adverse
656 experience. The adverse events most commonly associated with discontinuation were rash
657 (3.0%), dizziness (2.8%), and headache (2.5%).

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

660 ***Monotherapy in Adults:*** The most commonly observed ($\geq 5\%$) adverse experiences seen
661 in association with the use of LAMICTAL during the monotherapy phase of the controlled
662 trial in adults not seen at an equivalent rate in the control group were vomiting, coordination
663 abnormality, dyspepsia, nausea, dizziness, rhinitis, anxiety, insomnia, infection, pain, weight
664 decrease, chest pain, and dysmenorrhea. The most commonly observed ($\geq 5\%$) adverse
665 experiences associated with the use of LAMICTAL during the conversion to monotherapy

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666 (add-on) period, not seen at an equivalent frequency among low-dose valproate-treated
667 patients, were dizziness, headache, nausea, asthenia, coordination abnormality, vomiting,
668 rash, somnolence, diplopia, ataxia, accidental injury, tremor, blurred vision, insomnia,
669 nystagmus, diarrhea, lymphadenopathy, pruritus, and sinusitis.

670 Approximately 10% of the 420 adult patients who received LAMICTAL as monotherapy
671 in premarketing clinical trials discontinued treatment because of an adverse experience. The
672 adverse events most commonly associated with discontinuation were rash (4.5%), headache
673 (3.1%), and asthenia (2.4%).

674 ***Adjunctive Therapy in Pediatric Patients:*** The most commonly observed ($\geq 5\%$) adverse
675 experiences seen in association with the use of LAMICTAL as adjunctive treatment in
676 pediatric patients and not seen at an equivalent rate in the control group were infection,
677 vomiting, rash, fever, somnolence, accidental injury, dizziness, diarrhea, abdominal pain,
678 nausea, ataxia, tremor, asthenia, bronchitis, flu syndrome, and diplopia.

679 In 339 patients age 2 to 16 years, 4.2% of patients on LAMICTAL and 2.9% of patients
680 on placebo discontinued due to adverse experiences. The most commonly reported adverse
681 experiences that led to discontinuation were rash for patients treated with LAMICTAL and
682 deterioration of seizure control for patients treated with placebo.

683 Approximately 11.5% of the 1,081 pediatric patients who received LAMICTAL as
684 adjunctive therapy in premarketing clinical trials discontinued treatment because of an
685 adverse experience. The adverse events most commonly associated with discontinuation
686 were rash (4.4%), reaction aggravated (1.7%), and ataxia (0.6%).

687 **Incidence in Controlled Clinical Studies:** The prescriber should be aware that the figures
688 in Tables 4, 5, 6, and 7 cannot be used to predict the frequency of adverse experiences in the
689 course of usual medical practice where patient characteristics and other factors may differ
690 from those prevailing during clinical studies. Similarly, the cited frequencies cannot be
691 directly compared with figures obtained from other clinical investigations involving
692 different treatments, uses, or investigators. An inspection of these frequencies, however,
693 does provide the prescriber with one basis to estimate the relative contribution of drug and
694 nondrug factors to the adverse event incidences in the population studied.

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

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

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

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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

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

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

712

713 In a randomized, parallel study comparing placebo and 300 and 500 mg/day of
 714 LAMICTAL, some of the more common drug-related adverse events were dose related (see
 715 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)
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

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

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

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

750 ‡ Up to 500 mg/day.

751 § 1000 mg/day.

752

753 ***Incidence in Controlled Adjunctive Trials in Pediatric Patients:*** Table 7 lists adverse
754 events that occurred in at least 2% of 339 pediatric patients who received LAMICTAL up to
755 15 mg/kg per day or a maximum of 750 mg per day. Reported adverse events were classified
756 using COSTART terminology.

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**Table 7: Treatment-Emergent Adverse Event Incidence in Placebo-Controlled
 Adjunctive Trials in Pediatric Patients
 (Events in at least 2% of patients treated with LAMICTAL
 and numerically more frequent than in the placebo group.)**

Body System/ Adverse Experience	Percent of Patients Receiving LAMICTAL (n =168)	Percent of Patients Receiving Placebo (n =171)
Body as a whole		
Infection	20	17
Fever	15	14
Accidental injury	14	12
Abdominal pain	10	5
Asthenia	8	4
Flu syndrome	7	6
Pain	5	4
Facial edema	2	1
Photosensitivity	2	0
Cardiovascular		
Hemorrhage	2	1
Digestive		
Vomiting	20	16
Diarrhea	11	9
Nausea	10	2
Constipation	4	2
Dyspepsia	2	1
Tooth disorder	2	1
Hemic and lymphatic		
Lymphadenopathy	2	1
Metabolic and nutritional		
Edema	2	0
Nervous system		
Somnolence	17	15
Dizziness	14	4
Ataxia	11	3
Tremor	10	1
Emotional lability	4	2
Gait abnormality	4	2
Thinking abnormality	3	2

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Convulsions	2	1
Nervousness	2	1
Vertigo	2	1
Respiratory		
Pharyngitis	14	11
Bronchitis	7	5
Increased cough	7	6
Sinusitis	2	1
Brochospasm	2	1
Skin		
Rash	14	12
Eczema	2	1
Pruritus	2	1
Special Senses		
Diplopia	5	1
Blurred vision	4	1
Ear disorder	2	1
Vision abnormality	2	0
Urogenital		
Male and female patients		
Urinary tract infection	3	0
Male patients only	n = 93	n = 92
Penis disorder	2	0

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Other Adverse Events Observed During All Clinical Trials For Adult and Pediatric

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Patients: LAMICTAL has been administered to 3923 individuals for whom complete

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adverse event data was captured during all clinical trials, only some of which were placebo

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controlled. During these trials, all adverse events were recorded by the clinical investigators

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using terminology of their own choosing. To provide a meaningful estimate of the

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proportion of individuals having adverse events, similar types of events were grouped into a

770

smaller number of standardized categories using modified COSTART dictionary

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terminology. The frequencies presented represent the proportion of the 3923 individuals

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exposed to LAMICTAL who experienced an event of the type cited on at least one occasion

773

while receiving LAMICTAL. All reported events are included except those already listed in

774

the previous table, those too general to be informative, and those not reasonably associated

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with the use of the drug.

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Events are further classified within body system categories and enumerated in order of

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decreasing frequency using the following definitions: *frequent* adverse events are defined as

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778 those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in
779 1/100 to 1/1000 patients; *rare* adverse events are those occurring in fewer than 1/1000
780 patients.

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

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

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

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

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

797 **Hematologic and Lymphatic System: Infrequent:** Anemia, ecchymosis, leukocytosis,
798 leukopenia, lymphadenopathy, and petechia. **Rare:** Eosinophilia, fibrin decrease, fibrinogen
799 decrease, iron deficiency anemia, lymphocytosis, macrocytic anemia, and
800 thrombocytopenia.

801 **Metabolic and Nutritional Disorders: Infrequent:** Peripheral edema, weight gain, and
802 weight loss. **Rare:** Alcohol intolerance, alkaline phosphatase increase, bilirubinemia,
803 general edema, and hyperglycemia.

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

806 **Nervous System: Frequent:** Amnesia, confusion, hostility, memory decrease,
807 nervousness, nystagmus, thinking abnormality, and vertigo. **Infrequent:** Abnormal dreams,
808 abnormal gait, agitation, akathisia, apathy, aphasia, CNS depression, depersonalization,
809 dysarthria, dyskinesia, dysphoria, emotional lability, euphoria, faintness, grand mal
810 convulsions, hallucinations, hyperkinesia, hypertonia, hypesthesia, libido increased, mind
811 racing, muscle spasm, myoclonus, panic attack, paranoid reaction, personality disorder,
812 psychosis, sleep disorder, and stupor. **Rare:** Cerebrovascular accident, cerebellar syndrome,
813 cerebral sinus thrombosis, choreoathetosis, CNS stimulation, delirium, delusions, dystonia,
814 hemiplegia, hyperalgesia, hyperesthesia, hypoesthesia, hypokinesia, hypomania, hypotonia,
815 libido decreased, manic depression reaction, movement disorder, neuralgia, neurosis,
816 paralysis, and suicidal ideation.

817 **Respiratory System: Infrequent:** Dyspnea, epistaxis, and hyperventilation. **Rare:**

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818 Bronchospasm, hiccup, and sinusitis.

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

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

827 **Postmarketing and Other Experience:** In addition to the adverse experiences reported
828 during clinical testing of LAMICTAL, the following adverse experiences have been
829 reported in patients receiving marketed LAMICTAL and from worldwide noncontrolled
830 investigational use. These adverse experiences have not been listed above, and data are
831 insufficient to support an estimate of their incidence or to establish causation.

832 **Blood and Lymphatic:** Agranulocytosis, aplastic anemia, disseminated intravascular
833 coagulation, hemolytic anemia, neutropenia, pancytopenia, red cell aplasia.

834 **Gastrointestinal:** Esophagitis.

835 **Hepatobiliary Tract and Pancreas:** Pancreatitis.

836 **Immunologic:** Lupus-like reaction, vasculitis.

837 **Lower Respiratory:** Apnea.

838 **Musculoskeletal:** Rhabdomyolysis has been observed in patients experiencing
839 hypersensitivity reactions.

840 **Neurology:** Exacerbation of parkinsonian symptoms in patients with pre-existing
841 Parkinson's disease, tics.

842 **Non-site Specific:** Hypersensitivity reaction, multiorgan failure, progressive
843 immunosuppression.

844

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

847

848 **OVERDOSAGE:**

849 **Human Overdose Experience:** Overdoses involving quantities up to 15 g have been
850 reported for LAMICTAL, some of which have been fatal. Overdose has resulted in ataxia,
851 nystagmus, increased seizures, decreased level of consciousness, coma, and intraventricular
852 conduction delay.

853 **Management of Overdose:** There are no specific antidotes for LAMICTAL. Following a
854 suspected overdose, hospitalization of the patient is advised. General supportive care is
855 indicated, including frequent monitoring of vital signs and close observation of the patient.
856 If indicated, emesis should be induced or gastric lavage should be performed; usual
857 precautions should be taken to protect the airway. It should be kept in mind that lamotrigine

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858 is rapidly absorbed (see CLINICAL PHARMACOLOGY). It is uncertain whether
859 hemodialysis is an effective means of removing lamotrigine from the blood. In six renal
860 failure patients, about 20% of the amount of lamotrigine in the body was removed by
861 hemodialysis during a 4-hour session. A Poison Control Center should be contacted for
862 information on the management of overdosage of LAMICTAL.

863

864 **DOSAGE AND ADMINISTRATION:**

865 **Adjunctive Use:** LAMICTAL is indicated as adjunctive therapy for partial seizures in
866 adults and pediatric patients (≥ 2 years of age). LAMICTAL is also indicated as adjunctive
867 therapy for the generalized seizures of Lennox-Gastaut syndrome in adult and pediatric
868 patients (≥ 2 years of age).

869 **Monotherapy Use:** LAMICTAL is indicated for conversion to monotherapy in adults with
870 partial seizures who are receiving treatment with a single EIAED (e.g., carbamazepine,
871 phenytoin, phenobarbital, etc.).

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

876 **Safety and effectiveness in pediatric patients below the age of 16 years other than**
877 **those with partial seizures and the generalized seizures of Lennox-Gastaut syndrome**
878 **have not been established (see BOX WARNING).**

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

887 **Adjunctive Therapy With LAMICTAL:** This section provides specific dosing
888 recommendations for patients 2 to 12 years of age and patients greater than 12 years of age.
889 Within each of these age-groups, specific dosing recommendations are provided depending
890 upon whether or not the patient is receiving VPA (Tables 8 and 9 for patients 2 to 12 years
891 of age, Tables 10 and 11 for patients greater than 12 years of age). In addition, the section
892 provides a discussion of dosing for those patients receiving concomitant AEDs that have not
893 been systematically evaluated in combination with LAMICTAL.

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

896 **Patients 2 to 12 Years of Age:** Recommended dosing guidelines for LAMICTAL added
897 to an antiepileptic drug (AED) regimen containing VPA are summarized in Table 8

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898 Recommended dosing guidelines for LAMICTAL added to EIAEDs are summarized in
899 Table 9.

900 ***LAMICTAL Added to AEDs Other Than EIAEDs and VPA:*** The effect of AEDs
901 other than EIAEDs and VPA on the metabolism of LAMICTAL is not currently known.
902 Therefore, no specific dosing guidelines can be provided in that situation. Conservative
903 starting doses and dose escalations (as with concomitant VPA) would be prudent;
904 maintenance dosing would be expected to fall between the maintenance dose with VPA and
905 the maintenance dose without VPA, but with an EIAED.

906 Note that the starting doses and dose escalations listed in Tables 8 and 9 are different than
907 those used in clinical trials; however, the maintenance doses are the same as in clinical
908 trials. Smaller starting doses and slower dose escalations than those used in clinical trials are
909 recommended because of the suggestions that the risk of rash may be decreased by smaller
910 starting doses and slower dose escalations. Therefore, maintenance doses will take longer to
911 reach in clinical practice than in clinical trials. It may take several weeks to months to
912 achieve an individualized maintenance dose. Maintenance doses in patients weighing less
913 than 30 kg, regardless of age or concomitant AED, may need to be increased as much as
914 50%, based on clinical response.

915 **The smallest available strength of LAMICTAL Chewable Dispersible Tablets is**
916 **2 mg, and only whole tablets should be administered. If the calculated dose cannot be**
917 **achieved using whole tablets, the dose should be rounded down to the nearest whole**
918 **tablet (see HOW SUPPLIED and PATIENT INFORMATION for a description of the**
919 **LAMICTAL Chewable Dispersible Tablet available sizes).**

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

Weeks 1 and 2		0.15 mg/kg/day in one or two divided doses, rounded down to the nearest whole tablet. Only whole tablets should be used for dosing.	
Weeks 3 and 4		0.3 mg/kg/day in one or two divided doses, rounded down to the nearest whole tablet.	
Weight based dosing can be achieved by using the following guide:			
If the patient's weight is		Give this daily dose, using the most appropriate combination of Lamictal 2 mg and 5 mg tablets	
Greater than	And less than	Weeks 1 and 2	Weeks 3 and 4
6.7 kg	14 kg	2 mg every <i>other</i> day	2 mg every day
14.1 kg	27 kg	2 mg every day	4 mg every day
27.1 kg	34 kg	4 mg every day	8 mg every day
34.1 kg	40 kg	5 mg every day	10 mg every day
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 whole tablet, and add this amount to the previously administered daily dose. The usual maintenance dose in patients adding LAMICTAL to VPA alone ranges from 1 to 3 mg/kg/day. Maintenance doses in patients weighing less than 30 kg may need to be increased by as much as 50%, based on clinical response.			

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**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 whole tablet.	
Weeks 3 and 4		1.2 mg/kg/day in two divided doses, rounded down to the nearest whole tablet.	
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 whole tablet, and add this amount to the previously administered daily dose. Maintenance doses in patients weighing less than 30 kg may need to be increased by as much as 50%, based on clinical response.			

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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.

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930 **LAMICTAL Added to AEDs Other Than EIAEDs and VPA:** The effect of AEDs
931 other than EIAEDs and VPA on the metabolism of LAMICTAL is not currently known.
932 Therefore, no specific dosing guidelines can be provided in that situation. Conservative
933 starting doses and dose escalations (as with concomitant VPA) would be prudent;
934 maintenance dosing would be expected to fall between the maintenance dose with VPA and
935 the maintenance dose without VPA, but with an EIAED.

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**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 monotherapy with LAMICTAL 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.

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

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

Usual Maintenance Dose: The usual maintenance doses identified in the tables above are

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960 derived from dosing regimens employed in the placebo-controlled adjunctive studies in
961 which the efficacy of LAMICTAL was established. In patients receiving multidrug regimens
962 employing EIAEDs **without VPA**, maintenance doses of adjunctive LAMICTAL as high as
963 700 mg/day have been used. In patients receiving **VPA alone**, maintenance doses of
964 adjunctive LAMICTAL as high as 200 mg/day have been used. The advantage of using
965 doses above those recommended in the tables above has not been established in controlled
966 trials.

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

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

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

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

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

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

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

LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets
17-JAN-2003

992

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

995 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP**
996 **Controlled Room Temperature] in a dry place.**

997 LAMICTAL Tablets, 100 mg, peach, scored, shield-shaped tablets debossed with
998 "LAMICTAL" and "100", bottles of 100 (NDC 0173-0642-55).

999 LAMICTAL Tablets, 150 mg, cream, scored, shield-shaped tablets debossed with
1000 "LAMICTAL" and "150", bottles of 60 (NDC 0173-0643-60).

1001 LAMICTAL Tablets, 200 mg, blue, scored, shield-shaped tablets debossed with
1002 "LAMICTAL" and "200", bottles of 60 (NDC 0173-0644-60).

1003 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP**
1004 **Controlled Room Temperature] in a dry place and protect from light.**

1005 LAMICTAL Chewable Dispersible Tablets, 2 mg, white to off-white, round tablets
1006 debossed with "LTG" over "2", bottles of 30 (NDC 0173-0699-00). ORDER DIRECTLY
1007 FROM GLAXO WELLCOME, INC. 1-800-334-4153.

1008 LAMICTAL Chewable Dispersible Tablets, 5 mg, white to off-white, caplet-shaped
1009 tablets debossed with "GX CL2", bottles of 100 (NDC 0173-0526-00).

1010 LAMICTAL Chewable Dispersible Tablets, 25 mg, white, super elliptical-shaped tablets
1011 debossed with "GX CL5", bottles of 100 (NDC 0173-0527-00).

1012 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP**
1013 **Controlled Room Temperature] in a dry place.**

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1015 **PATIENT INFORMATION:** The following wording is contained in a separate leaflet
1016 provided for patients.

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Information for the Patient

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LAMICTAL® (lamotrigine) Tablets

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

 25 mg, white Imprinted with LAMICTAL 25	 100 mg, peach Imprinted with LAMICTAL 100	 150 mg, cream Imprinted with LAMICTAL 150	 200 mg, blue Imprinted with LAMICTAL 200
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1022

LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets
17-JAN-2003

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LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

 2 mg, white Imprinted with LTG 2	 5 mg, white Imprinted with GX CL2	 25 mg, white Imprinted with GX CL5
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NOTE: The pictures above show actual tablet shape and size and the wording describes the color and printing that is on each strength of LAMICTAL Tablets and Chewable Dispersible Tablets. Before taking your medicine, it is important to compare the tablets you receive from your doctor or pharmacist with these pictures to make sure you have received the correct medicine.

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Please read this leaflet carefully before you take LAMICTAL and read the leaflet provided with any refill, in case any information has changed. This leaflet provides a summary of the information about your medicine. Please do not throw away this leaflet until you have finished your medicine. This leaflet does not contain all the information about LAMICTAL and is not meant to take the place of talking with your doctor. If you have any questions about LAMICTAL, ask your doctor or pharmacist.

1038

Information About Your Medicine:

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

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1. The Purpose of Your Medicine:

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Lamotrigine is intended to be used either alone or in combination with other medicines to treat seizures in people 2 years or older. When taking lamotrigine, it is important to follow your doctor's instructions.

1045

2. Who Should Not Take LAMICTAL:

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

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3. Side Effects to Watch for:

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- Most people who take LAMICTAL tolerate it well. The most common side effects with LAMICTAL are dizziness, headache, blurred or double vision, lack of coordination, sleepiness, nausea, vomiting, and rash.
- Although most patients who develop rash while receiving LAMICTAL have mild to moderate symptoms, some individuals may develop a serious skin reaction that requires hospitalization. Rarely, deaths have been reported. These serious skin reactions are most likely to happen within the first 8 weeks of treatment with LAMICTAL. Serious skin reactions occur more often in children than in adults.
- Rashes may be more likely to occur if you: 1) take LAMICTAL in combination with valproic acid (DEPAKENE® or DEPAKOTE®), 2) take a higher starting dose of

LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets
17-JAN-2003

1058 LAMICTAL than your doctor prescribed, or 3) increase your dose of LAMICTAL faster
1059 than prescribed.

1060 • It is not possible to predict whether a mild rash will develop into a more serious reaction.
1061 **Therefore, if you experience a skin rash, hives, fever, swollen lymph glands, painful**
1062 **sores in the mouth or around the eyes, or swelling of lips or tongue, tell a doctor**
1063 **immediately, since these symptoms may be the first signs of a serious reaction. A**
1064 **doctor should evaluate your condition and decide if you should continue taking**
1065 **LAMICTAL.**

1066 ***4. The Use of LAMICTAL During Pregnancy and Breast-feeding:***

1067 The effects of LAMICTAL during pregnancy are not known at this time. If you are
1068 pregnant or are planning to become pregnant, talk to your doctor. Some LAMICTAL passes
1069 into breast milk and the effects of this on infants are unknown. Therefore, if you are
1070 breast-feeding, you should discuss this with your doctor to determine if you should continue
1071 to take LAMICTAL.

1072 ***5. How to Use LAMICTAL:***

- 1073 • It is important to take LAMICTAL exactly as instructed by your doctor. The dose of
1074 LAMICTAL must be increased slowly. It may take several weeks or months before your
1075 final dosage can be determined by your doctor, based on your response.
- 1076 • Do not increase your dose of LAMICTAL or take more frequent doses than those
1077 indicated by your doctor.
- 1078 • If you miss a dose of LAMICTAL, do not double your next dose.
- 1079 • Do NOT stop taking LAMICTAL or any of your other seizure medicines unless
1080 instructed by your doctor.
- 1081 • Use caution before driving a car or operating complex, hazardous machinery until you
1082 know if LAMICTAL affects your ability to perform these tasks.
- 1083 • Tell your doctor if your seizures get worse or if you have any new types of seizures.
- 1084 • Always tell your doctor and pharmacist if you are taking or plan to take any other
1085 prescription or over-the-counter medicines.

1086 ***6. How to Take LAMICTAL:***

1087 LAMICTAL Tablets should be swallowed whole. Chewing the tablets may leave a bitter
1088 taste.

1089 LAMICTAL Chewable Dispersible Tablets may be swallowed whole, chewed, or mixed
1090 in water or diluted fruit juice. If the tablets are chewed, consume a small amount of water or
1091 diluted fruit juice to aid in swallowing.

1092 To disperse LAMICTAL Chewable Dispersible Tablets, add the tablets to a small amount
1093 of liquid (1 teaspoon, or enough to cover the medication) in a glass or spoon. Approximately
1094 1 minute later, when the tablets are completely dispersed, mix the solution and take the
1095 entire amount immediately.

1096 ***7. Storing Your Medicine:***

1097 Store LAMICTAL at room temperature away from heat and light. Always keep your

LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets
17-JAN-2003

1098 medicines out of the reach of children.

1099 This medicine was prescribed for your use only to treat seizures. Do not give the drug to
1100 others.

1101 If your doctor decides to stop your treatment, do not keep any leftover medicine unless
1102 your doctor tells you to. Throw away your medicine as instructed.

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GlaxoSmithKline

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Research Triangle Park, NC 27709

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1113 (Date of Issue)

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LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets
17-JAN-2003

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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

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

 25 mg, white Imprinted with LAMICTAL 25	 100 mg, peach Imprinted with LAMICTAL 100	 150 mg, cream Imprinted with LAMICTAL 150	 200 mg, blue Imprinted with LAMICTAL 200
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LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

 2 mg, white Imprinted with LTG 2	 5 mg, white Imprinted with GX CL2	 25 mg, white Imprinted with GX CL5
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Information About Your Medicine:

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LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets
17-JAN-2003

1141 **1. The Purpose of Your Medicine:**

1142 Lamotrigine is intended to be used either alone or in combination with other medicines to
1143 treat seizures in people age 2 years or older. When taking lamotrigine, it is important to
1144 follow your doctor's instructions.

1145 **2. Who Should Not Take LAMICTAL:**

1146 You should not take LAMICTAL if you had an allergic reaction to it in the past.

1147 **3. Side Effects to Watch for:**

- 1148 • Most people who take LAMICTAL tolerate it well. The most common side effects with
1149 LAMICTAL are dizziness, headache, blurred or double vision, lack of coordination,
1150 sleepiness, nausea, vomiting, and rash.
- 1151 • Although most patients who develop rash while receiving LAMICTAL have mild to
1152 moderate symptoms, some individuals may develop a serious skin reaction that requires
1153 hospitalization. Rarely, deaths have been reported. These serious skin reactions are most
1154 likely to happen within the first 8 weeks of treatment with LAMICTAL. Serious skin
1155 reactions occur more often in children than in adults.
- 1156 • Rashes may be more likely to occur if you: 1) take LAMICTAL in combination with
1157 valproic acid (DEPAKENE® or DEPAKOTE®), 2) take a higher starting dose of
1158 LAMICTAL than your doctor prescribed, or 3) increase your dose of LAMICTAL faster
1159 than prescribed.
- 1160 • It is not possible to predict whether a mild rash will develop into a more serious reaction.
1161 **Therefore, if you experience a skin rash, hives, fever, swollen lymph glands, painful**
1162 **sores in the mouth or around the eyes, or swelling of lips or tongue, tell a doctor**
1163 **immediately, since these symptoms may be the first signs of a serious reaction. A**
1164 **doctor should evaluate your condition and decide if you should continue taking**
1165 **LAMICTAL.**

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1168 pregnant or are planning to become pregnant, talk to your doctor. Some LAMICTAL passes
1169 into breast milk and the effects of this on infants are unknown. Therefore, if you are
1170 breast-feeding, you should discuss this with your doctor to determine if you should continue
1171 to take LAMICTAL.

1172 **5. How to Use LAMICTAL:**

- 1173 • It is important to take LAMICTAL exactly as instructed by your doctor. The dose of
1174 LAMICTAL must be increased slowly. It may take several weeks or months before your
1175 final dosage can be determined by your doctor, based on your response.
- 1176 • Do not increase your dose of LAMICTAL or take more frequent doses than those
1177 indicated by your doctor.
- 1178 • If you miss a dose of lamotrigine, do not double your next dose.
- 1179 • Do NOT stop taking LAMICTAL or any of your other seizure medicines unless
1180 instructed by your doctor.

LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets
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- 1181 • Use caution before driving a car or operating complex, hazardous machinery until you
1182 know if LAMICTAL affects your ability to perform these tasks.
1183 • Tell your doctor if your seizures get worse or if you have any new types of seizures.
1184 • Always tell your doctor and pharmacist if you are taking or plan to take any other
1185 prescription or over-the-counter medicines.

1186 **6. How to Take LAMICTAL:**

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1188 taste.

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1190 in water or diluted fruit juice. If the tablets are chewed, consume a small amount of water or
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1195 entire amount immediately.

1196 **7. Storing Your Medicine:**

1197 Store LAMICTAL at room temperature away from heat and light. Always keep your
1198 medicines out of the reach of children.

1199 This medicine was prescribed for your use only to treat seizures. Do not give the drug to
1200 others.

1201 If your doctor decides to stop your treatment, do not keep any leftover medicine unless
1202 your doctor tells you to. Throw away your medicine as instructed.
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