

LAMICTAL[®]
(lamotrigine)
Tablets

LAMICTAL[®]
(lamotrigine)
Chewable Dispersible Tablets

SERIOUS RASHES REQUIRING HOSPITALIZATION AND DISCONTINUATION OF TREATMENT HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF LAMICTAL. THE INCIDENCE OF THESE RASHES, WHICH HAVE INCLUDED STEVENS-JOHNSON SYNDROME, IS APPROXIMATELY 0.8% (8 PER 1,000) IN PEDIATRIC PATIENTS (AGE <16 YEARS) RECEIVING LAMICTAL AS ADJUNCTIVE THERAPY FOR EPILEPSY AND 0.3% (3 PER 1,000) IN ADULTS ON ADJUNCTIVE THERAPY FOR EPILEPSY. IN CLINICAL TRIALS OF BIPOLAR AND OTHER MOOD DISORDERS, THE RATE OF SERIOUS RASH WAS 0.08% (0.8 PER 1,000) IN ADULT PATIENTS RECEIVING LAMICTAL AS INITIAL MONOTHERAPY AND 0.13% (1.3 PER 1,000) IN ADULT PATIENTS RECEIVING LAMICTAL AS ADJUNCTIVE THERAPY. IN A PROSPECTIVELY FOLLOWED COHORT OF 1,983 PEDIATRIC PATIENTS WITH EPILEPSY TAKING ADJUNCTIVE LAMICTAL, THERE WAS 1 RASH-RELATED DEATH. IN WORLDWIDE POSTMARKETING EXPERIENCE, RARE CASES OF TOXIC EPIDERMAL NECROLYSIS AND/OR RASH-RELATED DEATH HAVE BEEN REPORTED IN ADULT AND PEDIATRIC PATIENTS, BUT THEIR NUMBERS ARE TOO FEW TO PERMIT A PRECISE ESTIMATE OF THE RATE.

OTHER THAN AGE, THERE ARE AS YET NO FACTORS IDENTIFIED THAT ARE KNOWN TO PREDICT THE RISK OF OCCURRENCE OR THE SEVERITY OF RASH ASSOCIATED WITH LAMICTAL. THERE ARE SUGGESTIONS, YET TO BE PROVEN, THAT THE RISK OF RASH MAY ALSO BE INCREASED BY (1) COADMINISTRATION OF LAMICTAL WITH VALPROATE (INCLUDES VALPROIC ACID AND DIVALPROEX SODIUM), (2) EXCEEDING THE RECOMMENDED INITIAL DOSE OF LAMICTAL, OR (3) EXCEEDING THE RECOMMENDED DOSE ESCALATION FOR LAMICTAL. HOWEVER, CASES HAVE BEEN REPORTED IN THE ABSENCE OF THESE FACTORS.

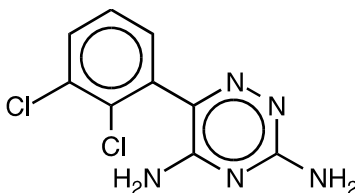
NEARLY ALL CASES OF LIFE-THREATENING RASHES ASSOCIATED WITH LAMICTAL HAVE OCCURRED WITHIN 2 TO 8 WEEKS OF TREATMENT INITIATION. HOWEVER, ISOLATED CASES HAVE BEEN REPORTED AFTER PROLONGED TREATMENT (E.G., 6 MONTHS). ACCORDINGLY, DURATION OF

40 **THERAPY CANNOT BE RELIED UPON AS A MEANS TO PREDICT THE**
41 **POTENTIAL RISK HERALDED BY THE FIRST APPEARANCE OF A RASH.**

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

50 **DESCRIPTION**

51 LAMICTAL (lamotrigine), an antiepileptic drug (AED) of the phenyltriazine class, is
52 chemically unrelated to existing antiepileptic drugs. Its chemical name is 3,5-diamino-6-(2,3-
53 dichlorophenyl)-*as*-triazine, its molecular formula is $C_9H_7N_5Cl_2$, and its molecular weight is
54 256.09. Lamotrigine is a white to pale cream-colored powder and has a pK_a of 5.7. Lamotrigine
55 is very slightly soluble in water (0.17 mg/mL at 25°C) and slightly soluble in 0.1 M HCl
56 (4.1 mg/mL at 25°C). The structural formula is:



58
59
60 LAMICTAL Tablets are supplied for oral administration as 25-mg (white), 100-mg (peach),
61 150-mg (cream), and 200-mg (blue) tablets. Each tablet contains the labeled amount of
62 lamotrigine and the following inactive ingredients: lactose; magnesium stearate; microcrystalline
63 cellulose; povidone; sodium starch glycolate; FD&C Yellow No. 6 Lake (100-mg tablet only);
64 ferric oxide, yellow (150-mg tablet only); and FD&C Blue No. 2 Lake (200-mg tablet only).

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

70 **CLINICAL PHARMACOLOGY**

71 **Mechanism of Action:** The precise mechanism(s) by which lamotrigine exerts its
72 anticonvulsant action are unknown. In animal models designed to detect anticonvulsant activity,
73 lamotrigine was effective in preventing seizure spread in the maximum electroshock (MES) and
74 pentylenetetrazol (scMet) tests, and prevented seizures in the visually and electrically evoked

75 after-discharge (EEAD) tests for antiepileptic activity. LAMICTAL also displayed inhibitory
76 properties in the kindling model in rats both during kindling development and in the fully
77 kindled state. The relevance of these models to human epilepsy, however, is not known.

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

83 The mechanisms by which lamotrigine exerts its therapeutic action in Bipolar Disorder have
84 not been established.

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 does
88 not exhibit high affinity binding (IC₅₀>100 μM) to the following neurotransmitter receptors:
89 adenosine A₁ and A₂; adrenergic α₁, α₂, and β; dopamine D₁ and D₂; γ-aminobutyric acid
90 (GABA) A and B; histamine H₁; kappa opioid; muscarinic acetylcholine; and serotonin 5-HT₂.
91 Studies have failed to detect an effect of lamotrigine on dihydropyridine-sensitive calcium
92 channels. It had weak effects at sigma opioid receptors (IC₅₀ = 145 μM). Lamotrigine did not
93 inhibit the uptake of norepinephrine, dopamine, or serotonin, (IC₅₀>200 μM) when tested in rat
94 synaptosomes and/or human platelets in vitro.

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

96 Lamotrigine did not inhibit N-methyl d-aspartate (NMDA)-induced depolarizations in rat cortical
97 slices or 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 NMDA-induced
100 currents (in the presence of 3 μM of glycine) in cultured hippocampal neurons exceeded
101 100 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. Inhibition
104 of this enzyme may interfere with the biosynthesis of nucleic acids and proteins. When oral daily
105 doses of lamotrigine were given to pregnant rats during organogenesis, fetal, placental, and
106 maternal folate concentrations were reduced. Significantly reduced concentrations of folate are
107 associated with teratogenesis (see PRECAUTIONS: Pregnancy). Folate concentrations were also
108 reduced in male rats given repeated oral doses of lamotrigine. Reduced concentrations were
109 partially returned to normal when supplemented with folic acid.

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

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

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

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

127

128 **Table 1. Mean* Pharmacokinetic Parameters in Healthy Volunteers and Adult Patients**
 129 **With Epilepsy**

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)	
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)
Healthy volunteers taking valproate:	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)
Patients with epilepsy taking valproate only:	Single-dose LAMICTAL	4	4.8 (1.8-8.4)	58.8 (30.5-88.8)	0.28 (0.16-0.40)
Patients with epilepsy taking carbamazepine, phenytoin, phenobarbital, or primidone [†] plus valproate:	Single-dose LAMICTAL	25	3.8 (1.0-10.0)	27.2 (11.2-51.6)	0.53 (0.27-1.04)
Patients with epilepsy taking carbamazepine, phenytoin, phenobarbital, or primidone [†] :	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)

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

135 † Carbamazepine, phenobarbital, phenytoin, and primidone have been shown to increase the
136 apparent clearance of lamotrigine. Estrogen-containing oral contraceptives and rifampin have
137 also been shown to increase the apparent clearance of lamotrigine (see CLINICAL
138 PHARMACOLOGY: Drug Interactions and PRECAUTIONS: Drug Interactions).

139

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

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

150 **Protein Binding:** Data from in vitro studies indicate that lamotrigine is approximately 55%
151 bound to human plasma proteins at plasma lamotrigine concentrations from 1 to 10 mcg/mL
152 (10 mcg/mL is 4 to 6 times the trough plasma concentration observed in the controlled efficacy
153 trials). Because lamotrigine is not highly bound to plasma proteins, clinically significant
154 interactions with other drugs through competition for protein binding sites are unlikely. The
155 binding of lamotrigine to plasma proteins did not change in the presence of therapeutic
156 concentrations of phenytoin, phenobarbital, or valproate. Lamotrigine did not displace other
157 AEDs (carbamazepine, phenytoin, phenobarbital) from protein binding sites.

158 **Drug Disposition:** Lamotrigine is metabolized predominantly by glucuronic acid
159 conjugation; the major metabolite is an inactive 2-N-glucuronide conjugate. After oral
160 administration of 240 mg of ¹⁴C-lamotrigine (15 μCi) to 6 healthy volunteers, 94% was
161 recovered in the urine and 2% was recovered in the feces. The radioactivity in the urine consisted
162 of unchanged lamotrigine (10%), the 2-N-glucuronide (76%), a 5-N-glucuronide (10%), a
163 2-N-methyl metabolite (0.14%), and other unidentified minor metabolites (4%).

164 **Drug Interactions: The apparent clearance of lamotrigine is affected by the**
165 **coadministration of certain medications.** Because lamotrigine is metabolized predominantly
166 by glucuronic acid conjugation, drugs that induce or inhibit glucuronidation may affect the
167 apparent clearance of lamotrigine.

168 Carbamazepine, phenytoin, phenobarbital, and primidone have been shown to increase the
169 apparent clearance of lamotrigine (see DOSAGE AND ADMINISTRATION and

170 PRECAUTIONS: Drug Interactions). Most clinical experience is derived from patients taking
171 these AEDs.

172 Estrogen-containing oral contraceptives and rifampin have also been shown to increase the
173 apparent clearance of lamotrigine (see PRECAUTIONS: Drug Interactions).

174 **Valproate decreases the apparent clearance of lamotrigine (i.e., more than doubles the**
175 **elimination half-life of lamotrigine), whether given with or without carbamazepine,**
176 **phenytoin, phenobarbital, or primidone.** Accordingly, if lamotrigine is to be administered to a
177 patient receiving valproate, lamotrigine must be given at a reduced dosage, of no more than half
178 the dose used in patients not receiving valproate, even in the presence of drugs that increase the
179 apparent clearance of lamotrigine (see DOSAGE AND ADMINISTRATION and
180 PRECAUTIONS: Drug Interactions).

181 The following drugs were shown not to increase the apparent clearance of lamotrigine:
182 felbamate, gabapentin, levetiracetam, oxcarbazepine, pregabalin, and topiramate. Zonisamide
183 does not appear to change the pharmacokinetic profile of lamotrigine (see PRECAUTIONS:
184 Drug Interactions).

185 In vitro inhibition experiments indicated that the formation of the primary metabolite of
186 lamotrigine, the 2-N-glucuronide, was not significantly affected by co-incubation with clozapine,
187 fluoxetine, phenelzine, risperidone, sertraline, or trazodone, and was minimally affected by co-
188 incubation with amitriptyline, bupropion, clonazepam, haloperidol, or lorazepam. In addition,
189 bufuralol metabolism data from human liver microsomes suggested that lamotrigine does not
190 inhibit the metabolism of drugs eliminated predominantly by CYP2D6.

191 LAMICTAL has no effects on the pharmacokinetics of lithium (see PRECAUTIONS: Drug
192 Interactions).

193 The pharmacokinetics of LAMICTAL were not changed by co-administration of bupropion
194 (see PRECAUTIONS: Drug Interactions).

195 Co-administration of olanzapine did not have a clinically relevant effect on LAMICTAL
196 pharmacokinetics (see PRECAUTIONS: Drug Interactions).

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

199 Following multiple administrations (150 mg twice daily) to normal volunteers taking no other
200 medications, lamotrigine induced its own metabolism, resulting in a 25% decrease in $t_{1/2}$ and a
201 37% increase in Cl/F at steady state compared to values obtained in the same volunteers
202 following a single dose. Evidence gathered from other sources suggests that self-induction by
203 LAMICTAL may not occur when LAMICTAL is given as adjunctive therapy in patients
204 receiving carbamazepine, phenytoin, phenobarbital, primidone, or rifampin.

205 **Dose Proportionality:** In healthy volunteers not receiving any other medications and given
206 single doses, the plasma concentrations of lamotrigine increased in direct proportion to the dose
207 administered over the range of 50 to 400 mg. In 2 small studies (n = 7 and 8) of patients with
208 epilepsy who were maintained on other AEDs, there also was a linear relationship between dose

209 and lamotrigine plasma concentrations at steady state following doses of 50 to 350 mg twice
210 daily.

211 **Elimination:** (see Table 1).

212 **Special Populations: Patients With Renal Insufficiency:** Twelve volunteers with
213 chronic renal failure (mean creatinine clearance = 13 mL/min; range = 6 to 23) and another
214 6 individuals undergoing hemodialysis were each given a single 100-mg dose of LAMICTAL.
215 The mean plasma half-lives determined in the study were 42.9 hours (chronic renal failure),
216 13.0 hours (during hemodialysis), and 57.4 hours (between hemodialysis) compared to
217 26.2 hours in healthy volunteers. On average, approximately 20% (range = 5.6 to 35.1) of the
218 amount of lamotrigine present in the body was eliminated by hemodialysis during a 4-hour
219 session.

220 **Hepatic Disease:** The pharmacokinetics of lamotrigine following a single 100-mg dose
221 of LAMICTAL were evaluated in 24 subjects with mild, moderate, and severe hepatic
222 dysfunction (Child-Pugh Classification system) and compared with 12 subjects without hepatic
223 impairment. The patients with severe hepatic impairment were without ascites (n = 2) or with
224 ascites (n = 5). The mean apparent clearance of lamotrigine in patients with mild (n = 12),
225 moderate (n = 5), severe without ascites (n = 2), and severe with ascites (n = 5) liver impairment
226 was 0.30 ± 0.09 , 0.24 ± 0.1 , 0.21 ± 0.04 , and 0.15 ± 0.09 mL/min/kg, respectively, as compared
227 to 0.37 ± 0.1 mL/min/kg in the healthy controls. Mean half-life of lamotrigine in patients with
228 mild, moderate, severe without ascites, and severe with ascites liver impairment was 46 ± 20 ,
229 72 ± 44 , 67 ± 11 , and 100 ± 48 hours, respectively, as compared to 33 ± 7 hours in healthy
230 controls (for dosing guidelines, see DOSAGE AND ADMINISTRATION: Patient With Hepatic
231 Impairment).

232 **Age: Pediatric Patients:** The pharmacokinetics of LAMICTAL following a single
233 2-mg/kg dose were evaluated in 2 studies of pediatric patients (n = 29 for patients aged
234 10 months to 5.9 years and n = 26 for patients aged 5 to 11 years). Forty-three patients received
235 concomitant therapy with other AEDs and 12 patients received LAMICTAL as monotherapy.
236 Lamotrigine pharmacokinetic parameters for pediatric patients are summarized in Table 2.

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

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 carbamazepine, phenytoin, phenobarbital, or primidone*	10	3.0 (1.0-5.9)	7.7 (5.7-11.4)	3.62 (2.44-5.28)
Patients taking antiepileptic drugs (AEDs) with no known effect on the apparent clearance of lamotrigine	7	5.2 (2.9-6.1)	19.0 (12.9-27.1)	1.2 (0.75-2.42)
Patients taking valproate 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 carbamazepine, phenytoin, phenobarbital, or primidone*	7	1.6 (1.0-3.0)	7.0 (3.8-9.8)	2.54 (1.35-5.58)
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone* plus valproate	8	3.3 (1.0-6.4)	19.1 (7.0-31.2)	0.89 (0.39-1.93)
Patients taking valproate 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 carbamazepine, phenytoin, phenobarbital, or primidone*	11	‡	‡	1.3
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone* plus valproate	8	‡	‡	0.5
Patients taking valproate only	4	‡	‡	0.3

251 *Carbamazepine, phenobarbital, phenytoin, and primidone have been shown to increase the
 252 apparent clearance of lamotrigine. Estrogen-containing oral contraceptives and rifampin have
 253 also been shown to increase the apparent clearance of lamotrigine (see CLINICAL
 254 PHARMACOLOGY: Drug Interactions and PRECAUTIONS: Drug Interactions).

255 [†]Two subjects were included in the calculation for mean T_{max}.

256 [‡]Parameter not estimated.

258 **Elderly:** The pharmacokinetics of lamotrigine following a single 150-mg dose of
259 LAMICTAL were evaluated in 12 elderly volunteers between the ages of 65 and 76 years (mean
260 creatinine clearance = 61 mL/min, range = 33 to 108 mL/min). The mean half-life of lamotrigine
261 in these subjects was 31.2 hours (range, 24.5 to 43.4 hours), and the mean clearance was
262 0.40 mL/min/kg (range, 0.26 to 0.48 mL/min/kg).

263 **Gender:** The clearance of lamotrigine is not affected by gender. However, during dose
264 escalation of LAMICTAL in one clinical trial in patients with epilepsy on a stable dose of
265 valproate (n = 77), mean trough lamotrigine concentrations, unadjusted for weight, were 24% to
266 45% higher (0.3 to 1.7 mcg/mL) in females than in males.

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

269 **CLINICAL STUDIES**

270 **Epilepsy:** The results of controlled clinical trials established the efficacy of LAMICTAL as
271 monotherapy in adults with partial onset seizures already receiving treatment with
272 carbamazepine, phenytoin, phenobarbital, or primidone as the single antiepileptic drug (AED), as
273 adjunctive therapy in adults and pediatric patients age 2 to 16 with partial seizures, and as
274 adjunctive therapy in the generalized seizures of Lennox-Gastaut syndrome in pediatric and adult
275 patients.

276 **Monotherapy With LAMICTAL in Adults With Partial Seizures Already Receiving**
277 **Treatment With Carbamazepine, Phenytoin, Phenobarbital, or Primidone as the**
278 **Single AED:** The effectiveness of monotherapy with LAMICTAL was established in a
279 multicenter, double-blind clinical trial enrolling 156 adult outpatients with partial seizures. The
280 patients experienced at least 4 simple partial, complex partial, and/or secondarily generalized
281 seizures during each of 2 consecutive 4-week periods while receiving carbamazepine or
282 phenytoin monotherapy during baseline. LAMICTAL (target dose of 500 mg/day) or valproate
283 (1,000 mg/day) was added to either carbamazepine or phenytoin monotherapy over a 4-week
284 period. Patients were then converted to monotherapy with LAMICTAL or valproate during the
285 next 4 weeks, then continued on monotherapy for an additional 12-week period.

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

293 The percentage of patients who met escape criteria was 42% (32/76) in the LAMICTAL
294 group and 69% (55/80) in the valproate group. The difference in the percentage of patients
295 meeting escape criteria was statistically significant (p = 0.0012) in favor of LAMICTAL. No
296 differences in efficacy based on age, sex, or race were detected.

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

301 ***Adjunctive Therapy With LAMICTAL in Adults With Partial Seizures:*** The
302 effectiveness of LAMICTAL as adjunctive therapy (added to other AEDs) was established in
303 3 multicenter, placebo-controlled, double-blind clinical trials in 355 adults with refractory partial
304 seizures. The patients had a history of at least 4 partial seizures per month in spite of receiving
305 one or more AEDs at therapeutic concentrations and, in 2 of the studies, were observed on their
306 established AED regimen during baselines that varied between 8 to 12 weeks. In the third,
307 patients were not observed in a prospective baseline. In patients continuing to have at least
308 4 seizures per month during the baseline, LAMICTAL or placebo was then added to the existing
309 therapy. In all 3 studies, change from baseline in seizure frequency was the primary measure of
310 effectiveness. The results given below are for all partial seizures in the intent-to-treat population
311 (all patients who received at least one dose of treatment) in each study, unless otherwise
312 indicated. The median seizure frequency at baseline was 3 per week while the mean at baseline
313 was 6.6 per week for all patients enrolled in efficacy studies.

314 One study (n = 216) was a double-blind, placebo-controlled, parallel trial consisting of a
315 24-week treatment period. Patients could not be on more than 2 other anticonvulsants and
316 valproate was not allowed. Patients were randomized to receive placebo, a target dose of
317 300 mg/day of LAMICTAL, or a target dose of 500 mg/day of LAMICTAL. The median
318 reductions in the frequency of all partial seizures relative to baseline were 8% in patients
319 receiving placebo, 20% in patients receiving 300 mg/day of LAMICTAL, and 36% in patients
320 receiving 500 mg/day of LAMICTAL. The seizure frequency reduction was statistically
321 significant in the 500-mg/day group compared to the placebo group, but not in the 300-mg/day
322 group.

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

329 The third study (n = 41) was a double-blind, placebo-controlled, crossover trial consisting of
330 two 12-week treatment periods separated by a 4-week washout period. Patients could not be on
331 more than 2 other anticonvulsants. Thirteen patients were on concomitant valproate; these
332 patients received 150 mg/day of LAMICTAL. The 28 other patients had a target dose of
333 300 mg/day of LAMICTAL. The median change in seizure frequency was a 26% reduction on
334 LAMICTAL compared to placebo (p<0.01).

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

337 **Adjunctive Therapy With LAMICTAL in Pediatric Patients With Partial Seizures:**

338 The effectiveness of LAMICTAL as adjunctive therapy in pediatric patients with partial seizures
339 was established in a multicenter, double-blind, placebo-controlled trial in 199 patients aged 2 to
340 16 years (n = 98 on LAMICTAL, n = 101 on placebo). Following an 8-week baseline phase,
341 patients were randomized to 18 weeks of treatment with LAMICTAL or placebo added to their
342 current AED regimen of up to 2 drugs. Patients were dosed based on body weight and valproate
343 use. Target doses were designed to approximate 5 mg/kg per day for patients taking valproate
344 (maximum dose, 250 mg/day) and 15 mg/kg per day for the patients not taking valproate
345 (maximum dose, 750 mg per day). The primary efficacy endpoint was percentage change from
346 baseline in all partial seizures. For the intent-to-treat population, the median reduction of all
347 partial seizures was 36% in patients treated with LAMICTAL and 7% on placebo, a difference
348 that was statistically significant ($p < 0.01$).

349 **Adjunctive Therapy With LAMICTAL in Pediatric and Adult Patients With**

350 **Lennox-Gastaut Syndrome:** The effectiveness of LAMICTAL as adjunctive therapy in
351 patients with Lennox-Gastaut syndrome was established in a multicenter, double-blind,
352 placebo-controlled trial in 169 patients aged 3 to 25 years (n = 79 on LAMICTAL, n = 90 on
353 placebo). Following a 4-week single-blind, placebo phase, patients were randomized to 16 weeks
354 of treatment with LAMICTAL or placebo added to their current AED regimen of up to 3 drugs.
355 Patients were dosed on a fixed-dose regimen based on body weight and valproate use. Target
356 doses were designed to approximate 5 mg/kg per day for patients taking valproate (maximum
357 dose, 200 mg/day) and 15 mg/kg per day for patients not taking valproate (maximum dose,
358 400 mg/day). The primary efficacy endpoint was percentage change from baseline in major
359 motor seizures (atonic, tonic, major myoclonic, and tonic-clonic seizures). For the intent-to-treat
360 population, the median reduction of major motor seizures was 32% in patients treated with
361 LAMICTAL and 9% on placebo, a difference that was statistically significant ($p < 0.05$). Drop
362 attacks were significantly reduced by LAMICTAL (34%) compared to placebo (9%), as were
363 tonic-clonic seizures (36% reduction versus 10% increase for LAMICTAL and placebo,
364 respectively).

365 **Adjunctive Therapy With LAMICTAL in Pediatric and Adult Patients With**

366 **Primary Generalized Tonic-Clonic Seizures:** The effectiveness of LAMICTAL as
367 adjunctive therapy in patients with primary generalized tonic-clonic seizures was established in a
368 multicenter, double-blind, placebo-controlled trial in 117 pediatric and adult patients ≥ 2 years
369 (n = 58 on LAMICTAL, n = 59 on placebo). Patients with at least 3 primary generalized tonic-
370 clonic seizures during an 8-week baseline phase were randomized to 19 to 24 weeks of treatment
371 with LAMICTAL or placebo added to their current AED regimen of up to 2 drugs. Patients were
372 dosed on a fixed-dose regimen, with target doses ranging from 3 mg/kg/day to 12 mg/kg/day for
373 pediatric patients and from 200 mg/day to 400 mg/day for adult patients based on concomitant
374 AED.

375 The primary efficacy endpoint was percentage change from baseline in primary generalized
376 tonic-clonic seizures. For the intent-to-treat population, the median percent reduction of primary

377 generalized tonic-clonic seizures was 66% in patients treated with LAMICTAL and 34% on
378 placebo, a difference that was statistically significant (p=0.006).

379
380 **Bipolar Disorder:** The effectiveness of LAMICTAL in the maintenance treatment of Bipolar I
381 Disorder was established in 2 multicenter, double-blind, placebo-controlled studies in adult
382 patients who met DSM-IV criteria for Bipolar I Disorder. Study 1 enrolled patients with a current
383 or recent (within 60 days) depressive episode as defined by DSM-IV and Study 2 included
384 patients with a current or recent (within 60 days) episode of mania or hypomania as defined by
385 DSM-IV. Both studies included a cohort of patients (30% of 404 patients in Study 1 and 28% of
386 171 patients in Study 2) with rapid cycling Bipolar Disorder (4 to 6 episodes per year).

387 In both studies, patients were titrated to a target dose of 200 mg of LAMICTAL, as add-on
388 therapy or as monotherapy, with gradual withdrawal of any psychotropic medications during an
389 8- to 16-week open-label period. Overall 81% of 1,305 patients participating in the open-label
390 period were receiving 1 or more other psychotropic medications, including benzodiazepines,
391 selective serotonin reuptake inhibitors (SSRIs), atypical antipsychotics (including olanzapine),
392 valproate, or lithium, during titration of LAMICTAL. Patients with a CGI-severity score of 3 or
393 less maintained for at least 4 continuous weeks, including at least the final week on monotherapy
394 with LAMICTAL, were randomized to a placebo-controlled, double-blind treatment period for
395 up to 18 months. The primary endpoint was TIME (time to intervention for a mood episode or
396 one that was emerging, time to discontinuation for either an adverse event that was judged to be
397 related to Bipolar Disorder, or for lack of efficacy). The mood episode could be depression,
398 mania, hypomania, or a mixed episode.

399 In Study 1, patients received double-blind monotherapy with LAMICTAL, 50 mg/day
400 (n = 50), LAMICTAL 200 mg/day (n = 124), LAMICTAL 400 mg/day (n = 47), or placebo
401 (n = 121). LAMICTAL (200- and 400-mg/day treatment groups combined) was superior to
402 placebo in delaying the time to occurrence of a mood episode. Separate analyses of the 200 and
403 400 mg/day dose groups revealed no added benefit from the higher dose.

404 In Study 2, patients received double-blind monotherapy with LAMICTAL (100 to
405 400 mg/day, n = 59), or placebo (n = 70). LAMICTAL was superior to placebo in delaying time
406 to occurrence of a mood episode. The mean LAMICTAL dose was about 211 mg/day.

407 Although these studies were not designed to separately evaluate time to the occurrence of
408 depression or mania, a combined analysis for the 2 studies revealed a statistically significant
409 benefit for LAMICTAL over placebo in delaying the time to occurrence of both depression and
410 mania, although the finding was more robust for depression.

411 **INDICATIONS AND USAGE**

412 **Epilepsy:**

413 **Adjunctive Use:** LAMICTAL is indicated as adjunctive therapy for partial seizures, the
414 generalized seizures of Lennox-Gastaut syndrome, and primary generalized tonic-clonic seizures
415 in adults and pediatric patients (≥2 years of age).

416

417 **Monotherapy Use:** LAMICTAL is indicated for conversion to monotherapy in adults with
418 partial seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital,
419 primidone, or valproate as the single AED.

420 Safety and effectiveness of LAMICTAL have not been established (1) as initial monotherapy,
421 (2) for conversion to monotherapy from AEDs other than carbamazepine, phenytoin,
422 phenobarbital, primidone, or valproate, or (3) for simultaneous conversion to monotherapy from
423 2 or more concomitant AEDs (see DOSAGE AND ADMINISTRATION).

424

425 **Bipolar Disorder:** LAMICTAL is indicated for the maintenance treatment of Bipolar I
426 Disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania,
427 mixed episodes) in patients treated for acute mood episodes with standard therapy. The
428 effectiveness of LAMICTAL in the acute treatment of mood episodes has not been established.

429 The effectiveness of LAMICTAL as maintenance treatment was established in
430 2 placebo-controlled trials of 18 months' duration in patients with Bipolar I Disorder as defined
431 by DSM-IV (see CLINICAL STUDIES, Bipolar Disorder). The physician who elects to use
432 LAMICTAL for periods extending beyond 18 months should periodically re-evaluate the
433 long-term usefulness of the drug for the individual patient.

434 **CONTRAINDICATIONS**

435 LAMICTAL is contraindicated in patients who have demonstrated hypersensitivity to the drug
436 or its ingredients.

437 **WARNINGS**

438 **SEE BOX WARNING REGARDING THE RISK OF SERIOUS RASHES REQUIRING**
439 **HOSPITALIZATION AND DISCONTINUATION OF LAMICTAL.**

440 **ALTHOUGH BENIGN RASHES ALSO OCCUR WITH LAMICTAL, IT IS NOT**
441 **POSSIBLE TO PREDICT RELIABLY WHICH RASHES WILL PROVE TO BE**
442 **SERIOUS OR LIFE THREATENING. ACCORDINGLY, LAMICTAL SHOULD**
443 **ORDINARILY BE DISCONTINUED AT THE FIRST SIGN OF RASH, UNLESS THE**
444 **RASH IS CLEARLY NOT DRUG RELATED. DISCONTINUATION OF TREATMENT**
445 **MAY NOT PREVENT A RASH FROM BECOMING LIFE THREATENING OR**
446 **PERMANENTLY DISABLING OR DISFIGURING.**

447 **Serious Rash: Pediatric Population:** The incidence of serious rash associated with
448 hospitalization and discontinuation of LAMICTAL in a prospectively followed cohort of
449 pediatric patients with epilepsy receiving adjunctive therapy was approximately 0.8% (16 of
450 1,983). When 14 of these cases were reviewed by 3 expert dermatologists, there was
451 considerable disagreement as to their proper classification. To illustrate, one dermatologist
452 considered none of the cases to be Stevens-Johnson syndrome; another assigned 7 of the 14 to
453 this diagnosis. There was 1 rash-related death in this 1,983 patient cohort. Additionally, there

454 have been rare cases of toxic epidermal necrolysis with and without permanent sequelae and/or
455 death in US and foreign postmarketing experience.

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

460 **Adult Population:** Serious rash associated with hospitalization and discontinuation of
461 LAMICTAL occurred in 0.3% (11 of 3,348) of adult patients who received LAMICTAL in
462 premarketing clinical trials of epilepsy. In the bipolar and other mood disorders clinical trials, the
463 rate of serious rash was 0.08% (1 of 1,233) of adult patients who received LAMICTAL as initial
464 monotherapy and 0.13% (2 of 1,538) of adult patients who received LAMICTAL as adjunctive
465 therapy. No fatalities occurred among these individuals. However, in worldwide postmarketing
466 experience, rare cases of rash-related death have been reported, but their numbers are too few to
467 permit a precise estimate of the rate.

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

472 There is evidence that the inclusion of valproate in a multidrug regimen increases the risk of
473 serious, potentially life-threatening rash in adults. Specifically, of 584 patients administered
474 LAMICTAL with valproate in epilepsy clinical trials, 6 (1%) were hospitalized in association
475 with rash; in contrast, 4 (0.16%) of 2,398 clinical trial patients and volunteers administered
476 LAMICTAL in the absence of valproate were hospitalized.

477 Other examples of serious and potentially life-threatening rash that did not lead to
478 hospitalization also occurred in premarketing development. Among these, 1 case was reported to
479 be Stevens-Johnson–like.

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

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

491 **Acute Multiorgan Failure:** Multiorgan failure, which in some cases has been fatal or
492 irreversible, has been observed in patients receiving LAMICTAL. Fatalities associated with
493 multiorgan failure and various degrees of hepatic failure have been reported in 2 of 3,796 adult

494 patients and 4 of 2,435 pediatric patients who received LAMICTAL in clinical trials. No such
495 fatalities have been reported in bipolar patients in clinical trials. Rare fatalities from multiorgan
496 failure have also been reported in compassionate plea and postmarketing use. The majority of
497 these deaths occurred in association with other serious medical events, including status
498 epilepticus and overwhelming sepsis, and hantavirus making it difficult to identify the initial
499 cause.

500 Additionally, 3 patients (a 45-year-old woman, a 3.5-year-old boy, and an 11-year-old girl)
501 developed multiorgan dysfunction and disseminated intravascular coagulation 9 to 14 days after
502 LAMICTAL was added to their AED regimens. Rash and elevated transaminases were also
503 present in all patients and rhabdomyolysis was noted in 2 patients. Both pediatric patients were
504 receiving concomitant therapy with valproate, while the adult patient was being treated with
505 carbamazepine and clonazepam. All patients subsequently recovered with supportive care after
506 treatment with LAMICTAL was discontinued.

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

510 **Withdrawal Seizures:** As with other AEDs, LAMICTAL should not be abruptly discontinued.
511 In patients with epilepsy there is a possibility of increasing seizure frequency. In clinical trials in
512 patients with Bipolar Disorder, 2 patients experienced seizures shortly after abrupt withdrawal of
513 LAMICTAL. However, there were confounding factors that may have contributed to the
514 occurrence of seizures in these bipolar patients. Unless safety concerns require a more rapid
515 withdrawal, the dose of LAMICTAL should be tapered over a period of at least 2 weeks (see
516 DOSAGE AND ADMINISTRATION).

517 **PRECAUTIONS**

518

519 **Concomitant Use With Oral Contraceptives:** Some estrogen-containing oral
520 contraceptives have been shown to decrease serum concentrations of lamotrigine (see
521 PRECAUTIONS: Drug Interactions). **Dosage adjustments will be necessary in most patients**
522 **who start or stop estrogen-containing oral contraceptives while taking LAMICTAL (see**
523 **DOSAGE AND ADMINISTRATION: Special Populations: Women and Oral**
524 **Contraceptives: Adjustments to the Maintenance Dose of LAMICTAL).** During the week of
525 inactive hormone preparation (“pill-free” week) of oral contraceptive therapy, plasma levels are
526 expected to rise, as much as doubling by the end of the week. Adverse events consistent with
527 elevated levels of lamotrigine, such as dizziness, ataxia, and diplopia, could occur.

528 **Dermatological Events (see BOX WARNING, WARNINGS):** Serious rashes associated
529 with hospitalization and discontinuation of LAMICTAL have been reported. Rare deaths have
530 been reported, but their numbers are too few to permit a precise estimate of the rate. There are
531 suggestions, yet to be proven, that the risk of rash may also be increased by (1) coadministration
532 of LAMICTAL with valproate, (2) exceeding the recommended initial dose of LAMICTAL, or

533 (3) exceeding the recommended dose escalation for LAMICTAL. However, cases have been
534 reported in the absence of these factors.

535 In epilepsy clinical trials, approximately 10% of all patients exposed to LAMICTAL
536 developed a rash. In the Bipolar Disorder clinical trials, 14% of patients exposed to LAMICTAL
537 developed a rash. Rashes associated with LAMICTAL do not appear to have unique identifying
538 features. Typically, rash occurs in the first 2 to 8 weeks following treatment initiation. However,
539 isolated cases have been reported after prolonged treatment (e.g., 6 months). Accordingly,
540 duration of therapy cannot be relied upon as a means to predict the potential risk heralded by the
541 first appearance of a rash.

542 Although most rashes resolved even with continuation of treatment with LAMICTAL, it is not
543 possible to predict reliably which rashes will prove to be serious or life threatening.

544 **ACCORDINGLY, LAMICTAL SHOULD ORDINARILY BE DISCONTINUED AT THE**
545 **FIRST SIGN OF RASH, UNLESS THE RASH IS CLEARLY NOT DRUG RELATED.**
546 **DISCONTINUATION OF TREATMENT MAY NOT PREVENT A RASH FROM**
547 **BECOMING LIFE THREATENING OR PERMANENTLY DISABLING OR**
548 **DISFIGURING.**

549 It is recommended that LAMICTAL not be restarted in patients who discontinued due to rash
550 associated with prior treatment with LAMICTAL unless the potential benefits clearly outweigh
551 the risks. If the decision is made to restart a patient who has discontinued LAMICTAL, the need
552 to restart with the initial dosing recommendations should be assessed. The greater the interval of
553 time since the previous dose, the greater consideration should be given to restarting with the
554 initial dosing recommendations. If a patient has discontinued LAMICTAL for a period of more
555 than 5 half-lives, it is recommended that initial dosing recommendations and guidelines be
556 followed. The half-life of LAMICTAL is affected by other concomitant medications (see
557 CLINICAL PHARMACOLOGY: Pharmacokinetics and Drug Metabolism, and DOSAGE AND
558 ADMINISTRATION).

559 **Use in Patients With Epilepsy:**

560 ***Sudden Unexplained Death in Epilepsy (SUDEP):*** During the premarketing
561 development of LAMICTAL, 20 sudden and unexplained deaths were recorded among a cohort
562 of 4,700 patients with epilepsy (5,747 patient-years of exposure).

563 Some of these could represent seizure-related deaths in which the seizure was not observed,
564 e.g., at night. This represents an incidence of 0.0035 deaths per patient-year. Although this rate
565 exceeds that expected in a healthy population matched for age and sex, it is within the range of
566 estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving
567 LAMICTAL (ranging from 0.0005 for the general population of patients with epilepsy, to 0.004
568 for a recently studied clinical trial population similar to that in the clinical development program
569 for LAMICTAL, to 0.005 for patients with refractory epilepsy). Consequently, whether these
570 figures are reassuring or suggest concern depends on the comparability of the populations
571 reported upon to the cohort receiving LAMICTAL and the accuracy of the estimates provided.
572 Probably most reassuring is the similarity of estimated SUDEP rates in patients receiving

573 LAMICTAL and those receiving another antiepileptic drug that underwent clinical testing in a
574 similar population at about the same time. Importantly, that drug is chemically unrelated to
575 LAMICTAL. This evidence suggests, although it certainly does not prove, that the high SUDEP
576 rates reflect population rates, not a drug effect.

577 **Status Epilepticus:** Valid estimates of the incidence of treatment emergent status
578 epilepticus among patients treated with LAMICTAL are difficult to obtain because reporters
579 participating in clinical trials did not all employ identical rules for identifying cases. At a
580 minimum, 7 of 2,343 adult patients had episodes that could unequivocally be described as status.
581 In addition, a number of reports of variably defined episodes of seizure exacerbation (e.g.,
582 seizure clusters, seizure flurries, etc.) were made.

583 **Use in Patients With Bipolar Disorder:**

584 **Acute Treatment of Mood Episodes:** Safety and effectiveness of LAMICTAL in the
585 acute treatment of mood episodes has not been established.

586 **Children and Adolescents (less than 18 years of age):** Treatment with
587 antidepressants is associated with an increased risk of suicidal thinking and behavior in children
588 and adolescents with major depressive disorder and other psychiatric disorders. It is not known
589 whether LAMICTAL is associated with a similar risk in this population (see PRECAUTIONS:
590 Clinical Worsening and Suicide Risk Associated With Bipolar Disorder).

591 Safety and effectiveness of LAMICTAL in patients below the age of 18 years with mood
592 disorders have not been established.

593 **Clinical Worsening and Suicide Risk Associated with Bipolar Disorder:**

594 Patients with bipolar disorder may experience worsening of their depressive symptoms and/or
595 the emergence of suicidal ideation and behaviors (suicidality) whether or not they are taking
596 medications for bipolar disorder. Patients should be closely monitored for clinical worsening
597 (including development of new symptoms) and suicidality, especially at the beginning of a
598 course of treatment, or at the time of dose changes.

599 In addition, patients with a history of suicidal behavior or thoughts, those patients exhibiting a
600 significant degree of suicidal ideation prior to commencement of treatment, and young adults,
601 are at an increased risk of suicidal thoughts or suicide attempts, and should receive careful
602 monitoring during treatment.

603 Patients (and caregivers of patients) should be alerted about the need to monitor for any
604 worsening of their condition (including development of new symptoms) and /or the emergence
605 of suicidal ideation/behavior or thoughts of harming themselves and to seek medical advice
606 immediately if these symptoms present.

607 Consideration should be given to changing the therapeutic regimen, including possibly
608 discontinuing the medication, in patients who experience clinical worsening (including
609 development of new symptoms) and/or the emergence of suicidal ideation/behavior especially if
610 these symptoms are severe, abrupt in onset, or were not part of the patient's presenting
611 symptoms.

612 Prescriptions for LAMICTAL should be written for the smallest quantity of tablets consistent
613 with good patient management, in order to reduce the risk of overdose. Overdoses have been
614 reported for LAMICTAL, some of which have been fatal (see OVERDOSAGE).

615 **Addition of LAMICTAL to a Multidrug Regimen That Includes Valproate (Dosage**
616 **Reduction):** Because valproate reduces the clearance of lamotrigine, the dosage of lamotrigine
617 in the presence of valproate is less than half of that required in its absence (see DOSAGE AND
618 ADMINISTRATION).

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

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

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

631 Because there is limited experience with the use of LAMICTAL in patients with impaired
632 liver function, the use in such patients may be associated with as yet unrecognized risks (see
633 CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

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

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

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

648 Patients should be advised that LAMICTAL may cause dizziness, somnolence, and other
649 symptoms and signs of central nervous system (CNS) depression. Accordingly, they should be
650 advised neither to drive a car nor to operate other complex machinery until they have gained

651 sufficient experience on LAMICTAL to gauge whether or not it adversely affects their mental
652 and/or motor performance.

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

656 Women should be advised to notify their physician if they plan to start or stop use of oral
657 contraceptives or other female hormonal preparations. Starting estrogen-containing oral
658 contraceptives may significantly decrease lamotrigine plasma levels and stopping estrogen-
659 containing oral contraceptives (including the “pill-free” week) may significantly increase
660 lamotrigine plasma levels (see PRECAUTIONS: Drug Interactions). Women should also be
661 advised to promptly notify their physician if they experience adverse events or changes in
662 menstrual pattern (e.g., break-through bleeding) while receiving LAMICTAL in combination
663 with these medications.

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

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

669 **Laboratory Tests:** The value of monitoring plasma concentrations of LAMICTAL has not
670 been established. Because of the possible pharmacokinetic interactions between LAMICTAL
671 and other drugs including AEDs (see Table 3), monitoring of the plasma levels of LAMICTAL
672 and concomitant drugs may be indicated, particularly during dosage adjustments. In general,
673 clinical judgment should be exercised regarding monitoring of plasma levels of LAMICTAL and
674 other drugs and whether or not dosage adjustments are necessary.

675

676 **Drug Interactions:**

677

678 The net effects of drug interactions with LAMICTAL are summarized in Table 3 (see also
679 DOSAGE AND ADMINISTRATION).

680

681 **Oral Contraceptives:** In 16 female volunteers, an oral contraceptive preparation containing
682 30 mcg ethinylestradiol and 150 mcg levonorgestrel increased the apparent clearance of
683 lamotrigine (300 mg/day) by approximately 2-fold with a mean decrease in AUC of 52% and in
684 C_{max} of 39%. In this study, trough serum lamotrigine concentrations gradually increased and
685 were approximately 2-fold higher on average at the end of the week of the inactive preparation
686 compared to trough lamotrigine concentrations at the end of the active hormone cycle.

687 Gradual transient increases in lamotrigine plasma levels (approximate 2-fold increase)
688 occurred during the week of inactive hormone preparation (“pill-free” week) for women not also
689 taking a drug that increased the clearance of lamotrigine (carbamazepine, phenytoin,
690 phenobarbital, primidone, or rifampin). The increase in lamotrigine plasma levels will be greater

691 if the dose of LAMICTAL is increased in the few days before or during the “pill-free” week.
692 Increases in lamotrigine plasma levels could result in dose-dependent adverse effects (see
693 PRECAUTIONS: Concomitant Use With Oral Contraceptives).

694 In the same study, co-administration of LAMICTAL (300 mg/day) in 16 female volunteers
695 did not affect the pharmacokinetics of the ethinylestradiol component of the oral contraceptive
696 preparation. There was a mean decrease in the AUC and C_{max} of the levonorgestrel component of
697 19% and 12%, respectively. Measurement of serum progesterone indicated that there was no
698 hormonal evidence of ovulation in any of the 16 volunteers, although measurement of serum
699 FSH, LH, and estradiol indicated that there was some loss of suppression of the hypothalamic-
700 pituitary-ovarian axis.

701 The effects of doses of LAMICTAL other than 300 mg/day have not been studied in clinical
702 trials.

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

707 Dosage adjustments will be necessary for most women receiving estrogen-containing oral
708 contraceptive preparations (see DOSAGE AND ADMINISTRATION: Special Populations:
709 Women and Oral Contraceptives).

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

716
717 **Bupropion:** The pharmacokinetics of a 100-mg single dose of LAMICTAL in healthy
718 volunteers (n = 12) were not changed by co-administration of bupropion sustained-release
719 formulation (150 mg twice a day) starting 11 days before LAMICTAL.

720 **Carbamazepine:** LAMICTAL has no appreciable effect on steady-state carbamazepine
721 plasma concentration. Limited clinical data suggest there is a higher incidence of dizziness,
722 diplopia, ataxia, and blurred vision in patients receiving carbamazepine with LAMICTAL than in
723 patients receiving other AEDs with LAMICTAL (see ADVERSE REACTIONS). The
724 mechanism of this interaction is unclear. The effect of LAMICTAL on plasma concentrations of
725 carbamazepine-epoxide is unclear. In a small subset of patients (n = 7) studied in a
726 placebo-controlled trial, LAMICTAL had no effect on carbamazepine-epoxide plasma
727 concentrations, but in a small, uncontrolled study (n = 9), carbamazepine-epoxide levels
728 increased.

729 The addition of carbamazepine decreases lamotrigine steady-state concentrations by
730 approximately 40%.

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

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

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

739 **Levetiracetam:** Potential drug interactions between levetiracetam and LAMICTAL were
740 assessed by evaluating serum concentrations of both agents during placebo-controlled clinical
741 trials. These data indicate that LAMICTAL does not influence the pharmacokinetics of
742 levetiracetam and that levetiracetam does not influence the pharmacokinetics of LAMICTAL.

743 **Lithium:** The pharmacokinetics of lithium were not altered in healthy subjects (n = 20) by
744 co-administration of LAMICTAL (100 mg/day) for 6 days.

745 **Olanzapine:** The AUC and C_{max} of olanzapine were similar following the addition of
746 olanzapine (15 mg once daily) to LAMICTAL (200 mg once daily) in healthy male volunteers
747 (n = 16) compared to the AUC and C_{max} in healthy male volunteers receiving olanzapine alone
748 (n = 16).

749 In the same study, the AUC and C_{max} of lamotrigine was reduced on average by 24% and
750 20%, respectively, following the addition of olanzapine to LAMICTAL in healthy male
751 volunteers compared to those receiving LAMICTAL alone. This reduction in lamotrigine plasma
752 concentrations is not expected to be clinically relevant.

753 **Oxcarbazepine:** The AUC and C_{max} of oxcarbazepine and its active 10-monohydroxy
754 oxcarbazepine metabolite were not significantly different following the addition of
755 oxcarbazepine (600 mg twice daily) to LAMICTAL (200 mg once daily) in healthy male
756 volunteers (n = 13) compared to healthy male volunteers receiving oxcarbazepine alone (n = 13).

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

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

764 **Phenytoin:** LAMICTAL has no appreciable effect on steady-state phenytoin plasma
765 concentrations in patients with epilepsy. The addition of phenytoin decreases lamotrigine steady-
766 state concentrations by approximately 40%.

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

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

773 **Topiramate:** Topiramate resulted in no change in plasma concentrations of lamotrigine.
 774 Administration of LAMICTAL resulted in a 15% increase in topiramate concentrations.

775 **Valproate:** When LAMICTAL was administered to healthy volunteers (n = 18) receiving
 776 valproate, the trough steady-state valproate plasma concentrations decreased by an average of
 777 25% over a 3-week period, and then stabilized. However, adding LAMICTAL to the existing
 778 therapy did not cause a change in valproate plasma concentrations in either adult or pediatric
 779 patients in controlled clinical trials.

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

784 **Zonisamide:** In a study of 18 patients with epilepsy, coadministration of zonisamide (200 to
 785 400 mg/day) with LAMICTAL (150 to 500 mg/day) for 35 days had no significant effect on the
 786 pharmacokinetics of lamotrigine.

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

792 **Other:** Results of in vitro experiments suggest that clearance of lamotrigine is unlikely to be
 793 reduced by concomitant administration of amitriptyline, clonazepam, clozapine, fluoxetine,
 794 haloperidol, lorazepam, phenelzine, risperidone, sertraline, or trazodone (see CLINICAL
 795 PHARMACOLOGY: Pharmacokinetics and Drug Metabolism). Results of in vitro
 796 experiments suggest that lamotrigine does not reduce the clearance of drugs eliminated
 797 predominantly by CYP2D6 (see CLINICAL PHARMACOLOGY).

798 .

799 **Table 3. Summary of Drug Interactions With LAMICTAL**

Drug	Drug Plasma Concentration With Adjunctive LAMICTAL*	Lamotrigine Plasma Concentration With Adjunctive Drugs†
Oral contraceptives (e.g., ethinylestradiol/levonorgestrel)‡	↔§	↓
Bupropion	Not assessed	↔
Carbamazepine (CBZ)	↔	↓
CBZ epoxide	?	
Felbamate	Not assessed	↔

Gabapentin	Not assessed	↔
Levetiracetam	↔	↔
Lithium	↔	Not assessed
Olanzapine	↔	↔ [¶]
Oxcarbazepine	↔	↔
10-monohydroxy oxcarbazepine metabolite [#]	↔	
Phenobarbital/primidone	↔	↓
Phenytoin (PHT)	↔	↓
Pregabalin	↔	↔
Rifampin	Not assessed	↓
Topiramate	↔ ^{**}	↔
Valproate	↓	↑
Valproate + PHT and/or CBZ	Not assessed	↔
Zonisamide	Not assessed	↔

800 * From adjunctive clinical trials and volunteer studies.

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

803 ‡ The effect of other hormonal contraceptive preparations or hormone replacement therapy on the
804 pharmacokinetics of lamotrigine has not been systematically evaluated in clinical trials and
805 the effect may not be similar to that seen with the ethinylestradiol/levonorgestrel
806 combinations.

807 § Modest decrease in levonorgestrel (see PRECAUTIONS: Drug Interactions: Effect of
808 LAMICTAL on Oral Contraceptives).

809 ¶ Not administered, but an active metabolite of carbamazepine.

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

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

812 ** Slight increase not expected to be clinically relevant.

813 ↔ = No significant effect.

814

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

816 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** No evidence of carcinogenicity
817 was seen in 1 mouse study or 2 rat studies following oral administration of lamotrigine for up to
818 2 years at maximum tolerated doses (30 mg/kg per day for mice and 10 to 15 mg/kg per day for
819 rats, doses that are equivalent to 90 mg/m² and 60 to 90 mg/m², respectively). Steady-state
820 plasma concentrations ranged from 1 to 4 mcg/mL in the mouse study and 1 to 10 mcg/mL in the
821 rat study. Plasma concentrations associated with the recommended human doses of 300 to
822 500 mg/day are generally in the range of 2 to 5 mcg/mL, but concentrations as high as
823 19 mcg/mL have been recorded.

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

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

832 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. No evidence of teratogenicity was
833 found in mice, rats, or rabbits when lamotrigine was orally administered to pregnant animals
834 during the period of organogenesis at doses up to 1.2, 0.5, and 1.1 times, respectively, on a
835 mg/m² basis, the highest usual human maintenance dose (i.e., 500 mg/day). However, maternal
836 toxicity and secondary fetal toxicity producing reduced fetal weight and/or delayed ossification
837 were seen in mice and rats, but not in rabbits at these doses. Teratology studies were also
838 conducted using bolus intravenous administration of the isethionate salt of lamotrigine in rats
839 and rabbits. In rat dams administered an intravenous dose at 0.6 times the highest usual human
840 maintenance dose, the incidence of intrauterine death without signs of teratogenicity was
841 increased.

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

848 Lamotrigine did not affect fertility, teratogenesis, or postnatal development when rats were
849 dosed prior to and during mating, and throughout gestation and lactation at doses equivalent to
850 0.4 times the highest usual human maintenance dose on a mg/m² basis.

851 When pregnant rats were orally dosed at 0.1, 0.14, or 0.3 times the highest human
852 maintenance dose (on a mg/m² basis) during the latter part of gestation (days 15 to 20), maternal
853 toxicity and fetal death were seen. In dams, food consumption and weight gain were reduced,
854 and the gestation period was slightly prolonged (22.6 vs. 22.0 days in the control group).
855 Stillborn pups were found in all 3 drug-treated groups with the highest number in the high-dose
856 group. Postnatal death was also seen, but only in the 2 highest doses, and occurred between day 1
857 and 20. Some of these deaths appear to be drug-related and not secondary to the maternal
858 toxicity. A no-observed-effect level (NOEL) could not be determined for this study.

859 Although LAMICTAL was not found to be teratogenic in the above studies, lamotrigine
860 decreases fetal folate concentrations in rats, an effect known to be associated with teratogenesis
861 in animals and humans. There are no adequate and well-controlled studies in pregnant women.
862 Because animal reproduction studies are not always predictive of human response, this drug

863 should be used during pregnancy only if the potential benefit justifies the potential risk to the
864 fetus.

865 **Non-Teratogenic Effects:** As with other antiepileptic drugs, physiological changes during
866 pregnancy may affect lamotrigine concentrations and/or therapeutic effect. There have been
867 reports of decreased lamotrigine concentrations during pregnancy and restoration of pre-partum
868 concentrations after delivery. Dosage adjustments may be necessary to maintain clinical
869 response.

870 **Pregnancy Exposure Registry:** To facilitate monitoring fetal outcomes of pregnant women
871 exposed to lamotrigine, physicians are encouraged to register patients, **before fetal outcome**
872 **(e.g., ultrasound, results of amniocentesis, birth, etc.) is known**, and can obtain information
873 by calling the Lamotrigine Pregnancy Registry at (800) 336-2176 (toll-free). Patients can enroll
874 themselves in the North American Antiepileptic Drug Pregnancy Registry by calling (888) 233-
875 2334 (toll-free).

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

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

880 **Pediatric Use:** LAMICTAL is indicated as adjunctive therapy for partial seizures, for the
881 generalized seizures of Lennox-Gastaut syndrome, and primary generalized tonic-clonic seizures
882 in patients above 2 years of age. .

883 Safety and effectiveness in patients below the age of 18 years with Bipolar Disorder has not
884 been established.

885 **Geriatric Use:** Clinical studies of LAMICTAL for epilepsy and in Bipolar Disorder did not
886 include sufficient numbers of subjects aged 65 and over to determine whether they respond
887 differently from younger subjects. In general, dose selection for an elderly patient should be
888 cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of
889 decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

890 **ADVERSE REACTIONS**

891 **SERIOUS RASH REQUIRING HOSPITALIZATION AND DISCONTINUATION OF**
892 **LAMICTAL, INCLUDING STEVENS-JOHNSON SYNDROME AND TOXIC**
893 **EPIDERMAL NECROLYSIS, HAVE OCCURRED IN ASSOCIATION WITH**
894 **THERAPY WITH LAMICTAL. RARE DEATHS HAVE BEEN REPORTED, BUT**
895 **THEIR NUMBERS ARE TOO FEW TO PERMIT A PRECISE ESTIMATE OF THE**
896 **RATE (see BOX WARNING).**

897 **Epilepsy:**

898 **Most Common Adverse Events in All Clinical Studies: Adjunctive Therapy in**
899 **Adults With Epilepsy:** The most commonly observed ($\geq 5\%$) adverse experiences seen in
900 association with LAMICTAL during adjunctive therapy in adults and not seen at an equivalent
901 frequency among placebo-treated patients were: dizziness, ataxia, somnolence, headache,

902 diplopia, blurred vision, nausea, vomiting, and rash. Dizziness, diplopia, ataxia, blurred vision,
903 nausea, and vomiting were dose related. Dizziness, diplopia, ataxia, and blurred vision occurred
904 more commonly in patients receiving carbamazepine with LAMICTAL than in patients receiving
905 other AEDs with LAMICTAL. Clinical data suggest a higher incidence of rash, including serious
906 rash, in patients receiving concomitant valproate than in patients not receiving valproate (see
907 WARNINGS).

908 Approximately 11% of the 3,378 adult patients who received LAMICTAL as adjunctive
909 therapy in premarketing clinical trials discontinued treatment because of an adverse experience.
910 The adverse events most commonly associated with discontinuation were rash (3.0%), dizziness
911 (2.8%), and headache (2.5%).

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

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

924 Approximately 10% of the 420 adult patients who received LAMICTAL as monotherapy in
925 premarketing clinical trials discontinued treatment because of an adverse experience. The
926 adverse events most commonly associated with discontinuation were rash (4.5%), headache
927 (3.1%), and asthenia (2.4%).

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

933 In 339 patients age 2 to 16 years with partial seizures or generalized seizures of Lennox-
934 Gastaut syndrome, 4.2% of patients on LAMICTAL and 2.9% of patients on placebo
935 discontinued due to adverse experiences. The most commonly reported adverse experiences that
936 led to discontinuation were rash for patients treated with LAMICTAL and deterioration of
937 seizure control for patients treated with placebo.

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

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

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

956 **Table 4. Treatment-Emergent Adverse Event Incidence in Placebo-Controlled**
 957 **Adjunctive Trials in Adult Patients With Epilepsy* (Events in at least 2% of patients**
 958 **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

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

959 * Patients in these adjunctive studies were receiving 1 to 3 of the following concomitant
960 AEDs (carbamazepine, phenytoin, phenobarbital, or primidone) in addition to LAMICTAL
961 or placebo. Patients may have reported multiple adverse experiences during the study or at
962 discontinuation; thus, patients may be included in more than one category.

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

965
966 In a randomized, parallel study comparing placebo and 300 and 500 mg/day of LAMICTAL,
967 some of the more common drug-related adverse events were dose related (see Table 5).

968

969 **Table 5. Dose-Related Adverse Events From a Randomized, Placebo-Controlled Trial**
 970 **in Adults With Epilepsy**

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*

971 *Significantly greater than placebo group (p<0.05).

972 †Significantly greater than group receiving LAMICTAL 300 mg (p<0.05).

973

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

977 The overall adverse experience profile for LAMICTAL was similar between females and
 978 males, and was independent of age. Because the largest non-Caucasian racial subgroup was only
 979 6% of patients exposed to LAMICTAL in placebo-controlled trials, there are insufficient data to
 980 support a statement regarding the distribution of adverse experience reports by race. Generally,
 981 females receiving either adjunctive LAMICTAL or placebo were more likely to report adverse
 982 experiences than males. The only adverse experience for which the reports on LAMICTAL were
 983 greater than 10% more frequent in females than males (without a corresponding difference by
 984 gender on placebo) was dizziness (difference = 16.5%). There was little difference between
 985 females and males in the rates of discontinuation of LAMICTAL for individual adverse
 986 experiences.

987 ***Incidence in a Controlled Monotherapy Trial in Adults With Partial Seizures:***

988 Table 6 lists treatment-emergent signs and symptoms that occurred in at least 5% of patients with
 989 epilepsy treated with monotherapy with LAMICTAL in a double-blind trial following
 990 discontinuation of either concomitant carbamazepine or phenytoin not seen at an equivalent
 991 frequency in the control group.

992

993 **Table 6. Treatment-Emergent Adverse Event Incidence in Adults With Partial Seizures in**
 994 **a Controlled Monotherapy Trial* (Events in at least 5% of patients treated with**
 995 **LAMICTAL and numerically more frequent than in the valproate group.)**

Body System/ Adverse Experience [†]	Percent of Patients Receiving LAMICTAL Monotherapy [‡] (n = 43)	Percent of Patients Receiving Low-Dose Valproate [§] Monotherapy (n = 44)
Body as a whole		
Pain	5	0
Infection	5	2
Chest pain	5	2
Digestive		
Vomiting	9	0
Dyspepsia	7	2
Nausea	7	2
Metabolic and nutritional		
Weight decrease	5	2
Nervous		
Coordination abnormality	7	0
Dizziness	7	0
Anxiety	5	0
Insomnia	5	2
Respiratory		
Rhinitis	7	2
Urogenital (female patients only)	(n = 21)	(n = 28)
Dysmenorrhea	5	0

996 * Patients in these studies were converted to LAMICTAL or valproate monotherapy from
 997 adjunctive therapy with carbamazepine or phenytoin. Patients may have reported multiple
 998 adverse experiences during the study; thus, patients may be included in more than one
 999 category.

1000 † Adverse experiences reported by at least 5% of patients are included.

1001 ‡ Up to 500 mg/day.

1002 § 1,000 mg/day.

1003

1004 Adverse events that occurred with a frequency of less than 5% and greater than 2% of patients
 1005 receiving LAMICTAL and numerically more frequent than placebo were:

1006 **Body as a Whole:** Asthenia, fever.
 1007 **Digestive:** Anorexia, dry mouth, rectal hemorrhage, peptic ulcer.
 1008 **Metabolic and Nutritional:** Peripheral edema.
 1009 **Nervous System:** Amnesia, ataxia, depression, hypesthesia, libido increase, decreased
 1010 reflexes, increased reflexes, nystagmus, irritability, suicidal ideation.
 1011 **Respiratory:** Epistaxis, bronchitis, dyspnea.
 1012 **Skin and Appendages:** Contact dermatitis, dry skin, sweating.
 1013 **Special Senses:** Vision abnormality.

1014 **Incidence in Controlled Adjunctive Trials in Pediatric Patients With Epilepsy:**

1015 Table 7 lists adverse events that occurred in at least 2% of 339 pediatric patients with partial
 1016 seizures or generalized seizures of Lennox-Gastaut syndrome, who received LAMICTAL up to
 1017 15 mg/kg per day or a maximum of 750 mg per day. Reported adverse events were classified
 1018 using COSTART terminology.

1019

1020 **Table 7. Treatment-Emergent Adverse Event Incidence in Placebo-Controlled Adjunctive**
 1021 **Trials in Pediatric Patients With Epilepsy (Events in at least 2% of patients treated with**
 1022 **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
Convulsions	2	1
Nervousness	2	1
Vertigo	2	1
Respiratory		
Pharyngitis	14	11
Bronchitis	7	5
Increased cough	7	6
Sinusitis	2	1
Bronchospasm	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

Visual abnormality	2	0
Urogenital		
Male and female patients		
Urinary tract infection	3	0
Male patients only	n = 93	n = 92
Penis disorder	2	0

1023
1024 **Bipolar Disorder:** The most commonly observed ($\geq 5\%$) adverse experiences seen in
1025 association with the use of LAMICTAL as monotherapy (100 to 400 mg/day) in Bipolar
1026 Disorder in the 2 double-blind, placebo-controlled trials of 18 months' duration, and numerically
1027 more frequent than in placebo-treated patients are included in Table 8. Adverse events that
1028 occurred in at least 5% of patients and were numerically more common during the dose
1029 escalation phase of LAMICTAL in these trials (when patients may have been receiving
1030 concomitant medications) compared to the monotherapy phase were: headache (25%), rash
1031 (11%), dizziness (10%), diarrhea (8%), dream abnormality (6%), and pruritus (6%).

1032 During the monotherapy phase of the double-blind, placebo-controlled trials of 18 months'
1033 duration, 13% of 227 patients who received LAMICTAL (100 to 400 mg/day), 16% of
1034 190 patients who received placebo, and 23% of 166 patients who received lithium discontinued
1035 therapy because of an adverse experience. The adverse events which most commonly led to
1036 discontinuation of LAMICTAL were rash (3%) and mania/hypomania/mixed mood adverse
1037 events (2%). Approximately 16% of 2,401 patients who received LAMICTAL (50 to
1038 500 mg/day) for Bipolar Disorder in premarketing trials discontinued therapy because of an
1039 adverse experience; most commonly due to rash (5%) and mania/hypomania/mixed mood
1040 adverse events (2%).

1041 ***Incidence in Controlled Clinical Studies of LAMICTAL for the Maintenance***
1042 ***Treatment of Bipolar I Disorder:*** Table 8 lists treatment-emergent signs and symptoms that
1043 occurred in at least 5% of patients with Bipolar Disorder treated with LAMICTAL monotherapy
1044 (100 to 400 mg/day), following the discontinuation of other psychotropic drugs, in
1045 2 double-blind, placebo-controlled trials of 18 months' duration and were numerically more
1046 frequent than in the placebo group.

1047

1048 **Table 8. Treatment-Emergent Adverse Event Incidence in 2 Placebo-Controlled Trials**
 1049 **in Adults With Bipolar I Disorder* (Events in at least 5% of patients treated with**
 1050 **LAMICTAL monotherapy and numerically more frequent than in the placebo group.)**

Body System/ Adverse Experience†	Percent of Patients Receiving LAMICTAL n = 227	Percent of Patients Receiving Placebo n = 190
General		
Back pain	8	6
Fatigue	8	5
Abdominal pain	6	3
Digestive		
Nausea	14	11
Constipation	5	2
Vomiting	5	2
Nervous System		
Insomnia	10	6
Somnolence	9	7
Xerostomia (dry mouth)	6	4
Respiratory		
Rhinitis	7	4
Exacerbation of cough	5	3
Pharyngitis	5	4
Skin		
Rash (nonserious)‡	7	5

1051 * Patients in these studies were converted to LAMICTAL (100 to 400 mg/day) or placebo
 1052 monotherapy from add-on therapy with other psychotropic medications. Patients may
 1053 have reported multiple adverse experiences during the study; thus, patients may be
 1054 included in more than one category.

1055 † Adverse experiences reported by at least 5% of patients are included.

1056 ‡ In the overall bipolar and other mood disorders clinical trials, the rate of serious rash
 1057 was 0.08% (1 of 1,233) of adult patients who received LAMICTAL as initial
 1058 monotherapy and 0.13% (2 of 1,538) of adult patients who received LAMICTAL as
 1059 adjunctive therapy (see WARNINGS).

1060
 1061 These adverse events were usually mild to moderate in intensity.

1062 Other events that occurred in 5% or more patients but equally or more frequently in the
 1063 placebo group included: dizziness, mania, headache, infection, influenza, pain, accidental injury,
 1064 diarrhea, and dyspepsia.

1065 Adverse events that occurred with a frequency of less than 5% and greater than 1% of patients
 1066 receiving LAMICTAL and numerically more frequent than placebo were:

1067 **General:** Fever, neck pain.
1068 **Cardiovascular:** Migraine.
1069 **Digestive:** Flatulence.
1070 **Metabolic and Nutritional:** Weight gain, edema.
1071 **Musculoskeletal:** Arthralgia, myalgia.
1072 **Nervous System:** Amnesia, depression, agitation, emotional lability, dyspraxia, abnormal
1073 thoughts, dream abnormality, hypoesthesia.
1074 **Respiratory:** Sinusitis.
1075 **Urogenital:** Urinary frequency.
1076 **Adverse Events Following Abrupt Discontinuation:** In the 2 maintenance trials, there
1077 was no increase in the incidence, severity or type of adverse events in Bipolar Disorder patients
1078 after abruptly terminating LAMICTAL therapy. In clinical trials in patients with Bipolar
1079 Disorder, 2 patients experienced seizures shortly after abrupt withdrawal of LAMICTAL.
1080 However, there were confounding factors that may have contributed to the occurrence of seizures
1081 in these bipolar patients (see DOSAGE AND ADMINISTRATION).
1082 **Mania/Hypomania/Mixed Episodes:** During the double-blind, placebo-controlled clinical
1083 trials in Bipolar I Disorder in which patients were converted to LAMICTAL monotherapy (100
1084 to 400 mg/day) from other psychotropic medications and followed for durations up to 18 months,
1085 the rate of manic or hypomanic or mixed mood episodes reported as adverse experiences was 5%
1086 for patients treated with LAMICTAL (n = 227), 4% for patients treated with lithium (n = 166),
1087 and 7% for patients treated with placebo (n = 190). In all bipolar controlled trials combined,
1088 adverse events of mania (including hypomania and mixed mood episodes) were reported in 5%
1089 of patients treated with LAMICTAL (n = 956), 3% of patients treated with lithium (n = 280), and
1090 4% of patients treated with placebo (n = 803).
1091 The overall adverse event profile for LAMICTAL was similar between females and males,
1092 between elderly and nonelderly patients, and among racial groups.
1093 **Other Adverse Events Observed During All Clinical Trials For Pediatric and Adult**
1094 **Patients With Epilepsy or Bipolar Disorder and Other Mood Disorders:** LAMICTAL
1095 has been administered to 6,694 individuals for whom complete adverse event data was captured
1096 during all clinical trials, only some of which were placebo controlled. During these trials, all
1097 adverse events were recorded by the clinical investigators using terminology of their own
1098 choosing. To provide a meaningful estimate of the proportion of individuals having adverse
1099 events, similar types of events were grouped into a smaller number of standardized categories
1100 using modified COSTART dictionary terminology. The frequencies presented represent the
1101 proportion of the 6,694 individuals exposed to LAMICTAL who experienced an event of the
1102 type cited on at least one occasion while receiving LAMICTAL. All reported events are included
1103 except those already listed in the previous tables or elsewhere in the labeling, those too general
1104 to be informative, and those not reasonably associated with the use of the drug.
1105 Events are further classified within body system categories and enumerated in order of
1106 decreasing frequency using the following definitions: *frequent* adverse events are defined as

1107 those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100
1108 to 1/1,000 patients; *rare* adverse events are those occurring in fewer than 1/1,000 patients.

1109 **Body as a Whole: Infrequent:** Allergic reaction, chills, halitosis, and malaise. **Rare:**
1110 Abdomen enlarged, abscess, and suicide/suicide attempt.

1111 **Cardiovascular System: Infrequent:** Flushing, hot flashes, hypertension, palpitations,
1112 postural hypotension, syncope, tachycardia, and vasodilation. **Rare:** Angina pectoris, atrial
1113 fibrillation, deep thrombophlebitis, ECG abnormality, and myocardial infarction.

1114 **Dermatological: Infrequent:** Acne, alopecia, hirsutism, maculopapular rash, skin
1115 discoloration, and urticaria. **Rare:** Angioedema, erythema, exfoliative dermatitis, fungal
1116 dermatitis, herpes zoster, leukoderma, multiforme erythema, petechial rash, pustular rash,
1117 seborrhea, Stevens-Johnson syndrome, and vesiculobullous rash.

1118 **Digestive System: Infrequent:** Dysphagia, eructation, gastritis, gingivitis, increased
1119 appetite, increased salivation, liver function tests abnormal, and mouth ulceration. **Rare:**
1120 Gastrointestinal hemorrhage, glossitis, gum hemorrhage, gum hyperplasia, hematemesis,
1121 hemorrhagic colitis, hepatitis, melena, stomach ulcer, stomatitis, thirst, and tongue edema.

1122 **Endocrine System: Rare:** Goiter and hypothyroidism.

1123 **Hematologic and Lymphatic System: Infrequent:** Ecchymosis and leukopenia. **Rare:**
1124 Anemia, eosinophilia, fibrin decrease, fibrinogen decrease, iron deficiency anemia, leukocytosis,
1125 lymphocytosis, macrocytic anemia, petechia, and thrombocytopenia.

1126 **Metabolic and Nutritional Disorders: Infrequent:** Aspartate transaminase increased.
1127 **Rare:** Alcohol intolerance, alkaline phosphatase increase, alanine transaminase increase,
1128 bilirubinemia, general edema, gamma glutamyl transpeptidase increase, and hyperglycemia.

1129 **Musculoskeletal System: Infrequent:** Arthritis, leg cramps, myasthenia, and twitching.
1130 **Rare:** Bursitis, joint disorder, muscle atrophy, pathological fracture, and tendinous contracture.

1131 **Nervous System: Frequent:** Confusion and paresthesia. **Infrequent:** Akathisia, apathy,
1132 aphasia, CNS depression, depersonalization, dysarthria, dyskinesia, euphoria, hallucinations,
1133 hostility, hyperkinesia, hypertonia, libido decreased, memory decrease, mind racing, movement
1134 disorder, myoclonus, panic attack, paranoid reaction, personality disorder, psychosis, sleep
1135 disorder, stupor, and suicidal ideation. **Rare:** Cerebellar syndrome, cerebrovascular accident,
1136 cerebral sinus thrombosis, choreoathetosis, CNS stimulation, delirium, delusions, dysphoria,
1137 dystonia, extrapyramidal syndrome, faintness, grand mal convulsions, hemiplegia, hyperalgesia,
1138 hyperesthesia, hypokinesia, hypotonia, manic depression reaction, muscle spasm, neuralgia,
1139 neurosis, paralysis, and peripheral neuritis.

1140 **Respiratory System: Infrequent:** Yawn. **Rare:** Hiccup and hyperventilation.

1141 **Special Senses: Frequent:** Amblyopia. **Infrequent:** Abnormality of accommodation,
1142 conjunctivitis, dry eyes, ear pain, photophobia, taste perversion, and tinnitus. **Rare:** Deafness,
1143 lacrimation disorder, oscillopsia, parosmia, ptosis, strabismus, taste loss, uveitis, and visual field
1144 defect.

1145 **Urogenital System: Infrequent:** Abnormal ejaculation, breast pain, hematuria, impotence,
1146 menorrhagia, polyuria, urinary incontinence, and urine abnormality. **Rare:** Acute kidney failure,

1147 anorgasmia, breast abscess, breast neoplasm, creatinine increase, cystitis, dysuria, epididymitis,
1148 female lactation, kidney failure, kidney pain, nocturia, urinary retention, urinary urgency, and
1149 vaginal moniliasis.

1150 **Postmarketing and Other Experience:** In addition to the adverse experiences reported
1151 during clinical testing of LAMICTAL, the following adverse experiences have been reported in
1152 patients receiving marketed LAMICTAL and from worldwide noncontrolled investigational use.
1153 These adverse experiences have not been listed above, and data are insufficient to support an
1154 estimate of their incidence or to establish causation.

1155 **Blood and Lymphatic:** Agranulocytosis, aplastic anemia, disseminated intravascular
1156 coagulation, hemolytic anemia, neutropenia, pancytopenia, red cell aplasia.

1157 **Gastrointestinal:** Esophagitis.

1158 **Hepatobiliary Tract and Pancreas:** Pancreatitis.

1159 **Immunologic:** Lupus-like reaction, vasculitis.

1160 **Lower Respiratory:** Apnea.

1161 **Musculoskeletal:** Rhabdomyolysis has been observed in patients experiencing
1162 hypersensitivity reactions.

1163 **Neurology:** Exacerbation of parkinsonian symptoms in patients with pre-existing
1164 Parkinson's disease, tics.

1165 **Non-site Specific:** Hypersensitivity reaction, multiorgan failure, progressive
1166 immunosuppression.

1167 **DRUG ABUSE AND DEPENDENCE**

1168 The abuse and dependence potential of LAMICTAL have not been evaluated in human
1169 studies.

1170 **OVERDOSAGE**

1171 **Human Overdose Experience:** Overdoses involving quantities up to 15 g have been
1172 reported for LAMICTAL, some of which have been fatal. Overdose has resulted in ataxia,
1173 nystagmus, increased seizures, decreased level of consciousness, coma, and intraventricular
1174 conduction delay.

1175 **Management of Overdose:** There are no specific antidotes for LAMICTAL. Following a
1176 suspected overdose, hospitalization of the patient is advised. General supportive care is
1177 indicated, including frequent monitoring of vital signs and close observation of the patient. If
1178 indicated, emesis should be induced or gastric lavage should be performed; usual precautions
1179 should be taken to protect the airway. It should be kept in mind that lamotrigine is rapidly
1180 absorbed (see CLINICAL PHARMACOLOGY). It is uncertain whether hemodialysis is an
1181 effective means of removing lamotrigine from the blood. In 6 renal failure patients, about 20% of
1182 the amount of lamotrigine in the body was removed by hemodialysis during a 4-hour session. A
1183 Poison Control Center should be contacted for information on the management of overdosage of
1184 LAMICTAL.

1185 **DOSAGE AND ADMINISTRATION**

1186 **Epilepsy:**

1187 **Adjunctive Use:** LAMICTAL is indicated as adjunctive therapy for partial seizures, the
1188 generalized seizures of Lennox-Gastaut syndrome, and primary generalized tonic-clonic seizures
1189 in adult and pediatric patients (≥ 2 years of age).

1190 **Monotherapy Use:** LAMICTAL is indicated for conversion to monotherapy in adults with
1191 partial seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital,
1192 primidone, or valproate as the single AED.

1193 **Safety and effectiveness of LAMICTAL have not been established. (1) as initial**
1194 **monotherapy, (2) for conversion to monotherapy from AEDs other than carbamazepine,**
1195 **phenytoin, phenobarbital, primidone, or valproate, or (3) for simultaneous conversion to**
1196 **monotherapy from 2 or more concomitant AEDs.**

1197
1198 **Bipolar Disorder:** LAMICTAL is indicated for the maintenance treatment of Bipolar I
1199 Disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania,
1200 mixed episodes) in patients treated for acute mood episodes with standard therapy. The
1201 effectiveness of LAMICTAL in the acute treatment of mood episodes has not been established.

1202 **General Dosing Considerations for Epilepsy and Bipolar Disorder Patients:** The
1203 risk of nonserious rash is increased when the recommended initial dose and/or the rate of dose
1204 escalation of LAMICTAL is exceeded. There are suggestions, yet to be proven, that the risk of
1205 severe, potentially life-threatening rash may be increased by (1) coadministration of LAMICTAL
1206 with valproate, (2) exceeding the recommended initial dose of LAMICTAL, or (3) exceeding the
1207 recommended dose escalation for LAMICTAL. However, cases have been reported in the
1208 absence of these factors (see **BOX WARNING**). Therefore, it is important that the dosing
1209 recommendations be followed closely.

1210 It is recommended that LAMICTAL not be restarted in patients who discontinued due to rash
1211 associated with prior treatment with LAMICTAL, unless the potential benefits clearly outweigh
1212 the risks. If the decision is made to restart a patient who has discontinued LAMICTAL, the need
1213 to restart with the initial dosing recommendations should be assessed. The greater the interval of
1214 time since the previous dose, the greater consideration should be given to restarting with the
1215 initial dosing recommendations. If a patient has discontinued LAMICTAL for a period of more
1216 than 5 half-lives, it is recommended that initial dosing recommendations and guidelines be
1217 followed.

1218
1219 **LAMICTAL Added to Drugs Known to Induce or Inhibit Glucuronidation:** Drugs
1220 other than those listed in PRECAUTIONS: Drug Interactions have not been systematically
1221 evaluated in combination with LAMICTAL. Since lamotrigine is metabolized predominantly by
1222 glucuronic acid conjugation, drugs that are known to induce or inhibit glucuronidation may
1223 affect the apparent clearance of lamotrigine, and doses of LAMICTAL may require adjustment
1224 based on clinical response.

1225 **Target Plasma Levels for Patients With Epilepsy or Bipolar Disorder:** A
1226 therapeutic plasma concentration range has not been established for lamotrigine. Dosing of
1227 LAMICTAL should be based on therapeutic response.

1228 The half-life of LAMICTAL is affected by other concomitant medications (see CLINICAL
1229 PHARMACOLOGY: Pharmacokinetics and Drug Metabolism).

1230 See also DOSAGE AND ADMINISTRATION: Special Populations.

1231 **Special Populations: Women and Oral Contraceptives: Starting LAMICTAL in**
1232 **Women Taking Oral Contraceptives:** Although estrogen-containing oral contraceptives
1233 have been shown to increase the clearance of lamotrigine (see PRECAUTIONS: Drug
1234 Interactions), no adjustments to the recommended dose escalation guidelines for LAMICTAL
1235 should be necessary solely based on the use of estrogen-containing oral contraceptives.
1236 Therefore, dose escalation should follow the recommended guidelines for initiating adjunctive
1237 therapy with LAMICTAL based on the concomitant AED (see Table 11). See below for
1238 adjustments to maintenance doses of LAMICTAL in women taking estrogen-containing oral
1239 contraceptives.

1240 **Adjustments to the Maintenance Dose of LAMICTAL: (1) Taking Estrogen-**
1241 **Containing Oral Contraceptives:** For women not taking carbamazepine, phenytoin,
1242 phenobarbital, primidone, or rifampin, the maintenance dose of LAMICTAL will in most cases
1243 need to be increased, by as much as 2-fold over the recommended target maintenance dose, in
1244 order to maintain a consistent lamotrigine plasma level (see PRECAUTIONS: Drug
1245 Interactions). **(2) Starting Estrogen-Containing Oral Contraceptives:** In women taking a stable
1246 dose of LAMICTAL and not taking carbamazepine, phenytoin, phenobarbital, primidone, or
1247 rifampin, the maintenance dose will in most cases need to be increased by as much as 2-fold, in
1248 order to maintain a consistent lamotrigine plasma level. The dose increases should begin at the
1249 same time that the oral contraceptive is introduced and continue, based on clinical response, no
1250 more rapidly than 50 to 100 mg/day every week. Dose increases should not exceed the
1251 recommended rate unless lamotrigine plasma levels or clinical response support larger increases
1252 (see Table 11, column 2). Gradual transient increases in lamotrigine plasma levels may occur
1253 during the week of inactive hormonal preparation (“pill-free” week), and these increases will be
1254 greater if dose increases are made in the days before or during the week of inactive hormonal
1255 preparation. Increased lamotrigine plasma levels could result in additional adverse events, such
1256 as dizziness, ataxia, and diplopia (see PRECAUTIONS: Drug Interactions). If adverse events
1257 attributable to LAMICTAL consistently occur during the “pill-free” week, dose adjustments to
1258 the overall maintenance dose may be necessary. Dose adjustments limited to the “pill-free” week
1259 are not recommended. For women taking LAMICTAL in addition to carbamazepine, phenytoin,
1260 phenobarbital, primidone, or rifampin, no adjustment should be necessary to the dose of
1261 LAMICTAL. **(3) Stopping Estrogen-Containing Oral Contraceptives:** For women not taking
1262 carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, the maintenance dose of
1263 LAMICTAL will in most cases need to be decreased by as much as 50%, in order to maintain a
1264 consistent lamotrigine plasma level. The decrease in dose of LAMICTAL should not exceed

1265 25% of the total daily dose per week over a 2-week period, unless clinical response or
1266 lamotrigine plasma levels indicate otherwise (see PRECAUTIONS: Drug Interactions). For
1267 women taking LAMICTAL in addition to carbamazepine, phenytoin, phenobarbital, primidone,
1268 or rifampin, no adjustment to the dose of LAMICTAL should be necessary.

1269 ***Women and Other Hormonal Contraceptive Preparations or Hormone***

1270 ***Replacement Therapy:*** The effect of other hormonal contraceptive preparations or hormone
1271 replacement therapy on the pharmacokinetics of lamotrigine has not been systematically
1272 evaluated. It has been reported that ethinylestradiol, not progestogens, increased the clearance of
1273 lamotrigine up to 2-fold, and the progestin only pills had no effect on lamotrigine plasma levels.
1274 Therefore, adjustments to the dosage of LAMICTAL in the presence of progestogens alone will
1275 likely not be needed.

1276 ***Patients With Hepatic Impairment:*** Experience in patients with hepatic impairment is
1277 limited. Based on a clinical pharmacology study in 24 patients with mild, moderate, and severe
1278 liver dysfunction (see CLINICAL PHARMACOLOGY), the following general
1279 recommendations can be made. No dosage adjustment is needed in patients with mild liver
1280 impairment. Initial, escalation, and maintenance doses should generally be reduced by
1281 approximately 25% in patients with moderate and severe liver impairment without ascites and
1282 50% in patients with severe liver impairment with ascites. Escalation and maintenance doses
1283 may be adjusted according to clinical response.

1284 ***Patients With Renal Functional Impairment:*** Initial doses of LAMICTAL should be
1285 based on patients' AED regimen (see above); reduced maintenance doses may be effective for
1286 patients with significant renal functional impairment (see CLINICAL PHARMACOLOGY).
1287 Few patients with severe renal impairment have been evaluated during chronic treatment with
1288 LAMICTAL. Because there is inadequate experience in this population, LAMICTAL should be
1289 used with caution in these patients.

1290 ***Epilepsy:***

1291 ***Adjunctive Therapy With LAMICTAL for Epilepsy:*** This section provides specific
1292 dosing recommendations for patients 2 to 12 years of age and patients greater than 12 years of
1293 age. Within each of these age-groups, specific dosing recommendations are provided depending
1294 upon concomitant AED (Table 9 for patients 2 to 12 years of age and Table 11 for patients
1295 greater than 12 years of age). A weight based dosing guide for pediatric patients on concomitant
1296 valproate is provided in Table 10.

1297 ***Patients 2 to 12 Years of Age:*** Recommended dosing guidelines are summarized in Table 9.

1298 Note that some of the starting doses and dose escalations listed in Table 9 are different than
1299 those used in clinical trials; however, the maintenance doses are the same as in clinical trials.
1300 Smaller starting doses and slower dose escalations than those used in clinical trials are
1301 recommended because of the suggestions that the risk of rash may be decreased by smaller
1302 starting doses and slower dose escalations. Therefore, maintenance doses will take longer to
1303 reach in clinical practice than in clinical trials. It may take several weeks to months to achieve an
1304 individualized maintenance dose. Maintenance doses in patients weighing less than 30 kg,

1305 regardless of age or concomitant AED, may need to be increased as much as 50%, based on
 1306 clinical response.

1307 **The smallest available strength of LAMICTAL Chewable Dispersible Tablets is 2 mg,**
 1308 **and only whole tablets should be administered. If the calculated dose cannot be achieved**
 1309 **using whole tablets, the dose should be rounded down to the nearest whole tablet (see**
 1310 **HOW SUPPLIED and PATIENT INFORMATION for a description of the available sizes**
 1311 **of LAMICTAL Chewable Dispersible Tablets).**

1312
 1313 **Table 9. Escalation Regimen for LAMICTAL in Patients 2 to 12 Years of Age With**
 1314 **Epilepsy**

	For Patients Taking Valproate (see Table 10 for weight-based dosing guide)	For Patients Taking AEDs Other Than Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate*	For Patients Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone* and Not Taking Valproate
Weeks 1 and 2	0.15 mg/kg/day in 1 or 2 divided doses, rounded down to the nearest whole tablet (see Table 10 for weight-based dosing guide).	0.3 mg/kg/day in 1 or 2 divided doses, rounded down to the nearest whole tablet.	0.6 mg/kg/day in 2 divided doses, rounded down to the nearest whole tablet.
Weeks 3 and 4	0.3 mg/kg/day in 1 or 2 divided doses, rounded down to the nearest whole tablet (see Table 10 for weight-based dosing guide).	0.6 mg/kg/day in 2 divided doses, rounded down to the nearest whole tablet.	1.2 mg/kg/day in 2 divided doses, rounded down to the nearest whole tablet.
Weeks 5 onwards to maintenance	The dose 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 dose should be increased every 1 to 2 weeks as follows: calculate 0.6 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily dose	The dose 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

Usual Maintenance Dose	1 to 5 mg/kg/day (maximum 200 mg/day in 1 or 2 divided doses). 1 to 3 mg/kg/day with valproate alone	4.5 to 7.5 mg/kg/day (maximum 300 mg/day in 2 divided doses)	5 to 15 mg/kg/day (maximum 400 mg/day in 2 divided doses)
Maintenance dose in patients less than 30 kg	May need to be increased by as much as 50%, based on clinical response	May need to be increased by as much as 50%, based on clinical response	May need to be increased by as much as 50%, based on clinical response

1315 **Note: Only whole tablets should be used for dosing**

1316 * Rifampin and estrogen-containing oral contraceptives have also been shown to increase the
1317 apparent clearance of lamotrigine (see PRECAUTIONS: Drug Interactions).

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1320 **Table 10. The Initial Weight-Based Dosing Guide for Patients 2 to 12 Years Taking**
1321 **Valproate (Weeks 1 to 4) With Epilepsy**

:			
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

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Patients Over 12 Years of Age: Recommended dosing guidelines are summarized in Table 11.

1326 **Table 11. Escalation Regimen for LAMICTAL in Patients Over 12 Years of Age With**
 1327 **Epilepsy**

	For Patients Taking Valproate	For Patients Taking AEDs Other Than Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate*	For Patients Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone* and Not Taking Valproate
Weeks 1 and 2	25 mg every other day	25 mg every day	50 mg/day
Weeks 3 and 4	25 mg every day	50 mg/day	100 mg/day (in 2 divided doses)
Weeks 5 onwards to maintenance	Increase by 25 to 50 mg/day every 1 to 2 weeks	Increase by 50 mg/day every 1 to 2 weeks	Increase by 100 mg/day every 1 to 2 weeks.
Usual Maintenance Dose	100 to 400 mg/day (1 or 2 divided doses) 100 to 200 mg/day with valproate alone	225 to 375 mg/day (in 2 divided doses).	300 to 500 mg/day (in 2 divided doses).

1328 * Rifampin and estrogen-containing oral contraceptives have also been shown to increase the
 1329 apparent clearance of lamotrigine (see PRECAUTIONS: Drug Interactions).

1330
 1331
 1332 **Conversion From Adjunctive Therapy With Carbamazepine, Phenytoin,**
 1333 **Phenobarbital, Primidone, or Valproate as the Single AED to Monotherapy With**
 1334 **LAMICTAL in Patients ≥16 Years of Age With Epilepsy:** The goal of the transition
 1335 regimen is to effect the conversion to monotherapy with LAMICTAL under conditions that
 1336 ensure adequate seizure control while mitigating the risk of serious rash associated with the rapid
 1337 titration of LAMICTAL.

1338 The recommended maintenance dose of LAMICTAL as monotherapy is 500 mg/day given in
 1339 2 divided doses.

1340 To avoid an increased risk of rash, the recommended initial dose and subsequent dose
 1341 escalations of LAMICTAL should not be exceeded (see BOX WARNING).

1342 **Conversion From Adjunctive Therapy With Carbamazepine, Phenytoin,**
 1343 **Phenobarbital, or Primidone to Monotherapy With LAMICTAL:** After achieving a dose
 1344 of 500 mg/day of LAMICTAL according to Table 11, the concomitant AED should be
 1345 withdrawn by 20% decrements each week over a 4-week period. The regimen for the withdrawal
 1346 of the concomitant AED is based on experience gained in the controlled monotherapy clinical
 1347 trial.

1348 **Conversion from Adjunctive Therapy With Valproate to Monotherapy With**
 1349 **LAMICTAL:** The conversion regimen involves 4 steps (see Table 12).

1350
 1351 **Table 12. Conversion From Adjunctive Therapy With Valproate to Monotherapy With**
 1352 **LAMICTAL in Patients ≥16 Years of Age With Epilepsy**

	LAMICTAL	Valproate
Step 1	Achieve a dose of 200 mg/day according to guidelines in Table 11 (if not already on 200 mg/day).	Maintain previous stable dose.
Step 2	Maintain at 200 mg/day.	Decrease to 500 mg/day by decrements no greater than 500 mg/day per week and then maintain the dose of 500 mg/day for 1 week.
Step 3	Increase to 300 mg/day and maintain for 1 week.	Simultaneously decrease to 250 mg/day and maintain for 1 week.
Step 4	Increase by 100 mg/day every week to achieve maintenance dose of 500 mg/day.	Discontinue.

1353
 1354 **Conversion from Adjunctive Therapy With Antiepileptic Drugs Other Than**
 1355 **Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate to**
 1356 **Monotherapy With LAMICTAL:** No specific dosing guidelines can be provided for
 1357 conversion to monotherapy with LAMICTAL with AEDs other than carbamazepine,
 1358 phenobarbital, phenytoin, primidone, or valproate.

1359 **Usual Maintenance Dose for Epilepsy:** The usual maintenance doses identified in
 1360 Tables 9-11 are derived from dosing regimens employed in the placebo-controlled adjunctive
 1361 studies in which the efficacy of LAMICTAL was established. In patients receiving multidrug
 1362 regimens employing carbamazepine, phenytoin, phenobarbital, or primidone **without valproate**,
 1363 maintenance doses of adjunctive LAMICTAL as high as 700 mg/day have been used. In patients
 1364 receiving **valproate alone**, maintenance doses of adjunctive LAMICTAL as high as 200 mg/day
 1365 have been used. The advantage of using doses above those recommended in Tables 9-12 has not
 1366 been established in controlled trials.

1367 **Discontinuation Strategy for Patients With Epilepsy:** For patients receiving
 1368 LAMICTAL in combination with other AEDs, a reevaluation of all AEDs in the regimen should
 1369 be considered if a change in seizure control or an appearance or worsening of adverse
 1370 experiences is observed.

1371 If a decision is made to discontinue therapy with LAMICTAL, a step-wise reduction of dose
 1372 over at least 2 weeks (approximately 50% per week) is recommended unless safety concerns
 1373 require a more rapid withdrawal (see PRECAUTIONS).

1374 *Discontinuing carbamazepine, phenytoin, phenobarbital, or primidone should prolong the*
 1375 *half-life of lamotrigine; discontinuing valproate should shorten the half-life of lamotrigine.*

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Bipolar Disorder: The goal of maintenance treatment with LAMICTAL is to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy. The target dose of LAMICTAL is 200 mg/day (100 mg/day in patients taking valproate, which decreases the apparent clearance of lamotrigine, and 400 mg/day in patients not taking valproate and taking either Carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, which increase the apparent clearance of lamotrigine). In the clinical trials, doses up to 400 mg/day as monotherapy were evaluated, however, no additional benefit was seen at 400 mg/day compared to 200 mg/day (see CLINICAL STUDIES: Bipolar Disorder). Accordingly, doses above 200 mg/day are not recommended. Treatment with LAMICTAL is introduced, based on concurrent medications, according to the regimen outlined in Table 13. If other psychotropic medications are withdrawn following stabilization, the dose of LAMICTAL should be adjusted. For patients discontinuing valproate, the dose of LAMICTAL should be doubled over a 2-week period in equal weekly increments (see Table 14). For patients discontinuing carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, the dose of LAMICTAL should remain constant for the first week and then should be decreased by half over a 2-week period in equal weekly decrements (see Table 14). The dose of LAMICTAL may then be further adjusted to the target dose (200 mg) as clinically indicated.

Dosage adjustments will be necessary in most patients who start or stop estrogen-containing oral contraceptives while taking LAMICTAL (see DOSAGE AND ADMINISTRATION: Special Populations: Women and Oral Contraceptives: Adjustments to the Maintenance Dose of LAMICTAL).

If other drugs are subsequently introduced, the dose of LAMICTAL may need to be adjusted. In particular, the introduction of valproate requires reduction in the dose of LAMICTAL (see CLINICAL PHARMACOLOGY: Drug Interactions).

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

Table 13. Escalation Regimen for LAMICTAL for Patients With Bipolar Disorder*

	For Patients Not Taking Carbamazepine (or Other Enzyme-Inducing Drugs [†]) or Valproate [‡]	For Patients Taking Valproate [‡]	For Patients Taking Carbamazepine (or Other Enzyme-Inducing Drugs) and Not Taking Valproate [‡]
Weeks 1 and 2	25 mg daily	25 mg every <i>other day</i>	50 mg daily
Weeks 3 and 4	50 mg daily	25 mg daily	100 mg daily, in divided doses

Week 5	100 mg daily	50 mg daily	200 mg daily, in divided doses
Week 6	200 mg daily	100 mg daily	300 mg daily, in divided doses
Week 7	200 mg daily	100 mg daily	up to 400 mg daily, in divided doses

1405 *See CLINICAL PHARMACOLOGY: Drug Interactions and PRECAUTIONS: Drug
1406 Interactions for a description of known drug interactions.
1407 †Carbamazepine, phenytoin, phenobarbital, primidone, rifampin, have been shown to increase
1408 the apparent clearance of lamotrigine.
1409 ‡Valproate has been shown to decrease the apparent clearance of lamotrigine.

1410
1411 **Table 14. Adjustments to LAMICTAL Dosing for Patients With Bipolar Disorder**
1412 **Following Discontinuation of Psychotropic Medications***

	Discontinuation of Psychotropic Drugs (excluding Valproate‡, Carbamazepine, or Other Enzyme-Inducing Drugs†)	After Discontinuation of Valproate‡	After Discontinuation of Carbamazepine or Other Enzyme-Inducing Drugs†
		Current LAMICTAL dose (mg/day) 100	Current LAMICTAL dose (mg/day) 400
Week 1	Maintain current LAMICTAL dose	150	400
Week 2	Maintain current LAMICTAL dose	200	300
Week 3 onward	Maintain current LAMICTAL dose	200	200

1413 *See CLINICAL PHARMACOLOGY: Drug Interactions and PRECAUTIONS: Drug
1414 Interactions for a description of known drug interactions.
1415 †Carbamazepine, phenytoin, phenobarbital, primidone, rifampin, have been shown to increase
1416 the apparent clearance of lamotrigine.
1417 ‡Valproate has been shown to decrease the apparent clearance of lamotrigine.

1418
1419 There is no body of evidence available to answer the question of how long the patient should
1420 remain on LAMICTAL therapy. Systematic evaluation of the efficacy of LAMICTAL in patients
1421 with either depression or mania who responded to standard therapy during an acute 8 to 16 week
1422 treatment phase and were then randomized to LAMICTAL or placebo for up to 76 weeks of
1423 observation for affective relapse demonstrated a benefit of such maintenance treatment (see

1424 CLINICAL STUDIES: Bipolar Disorder). Nevertheless, patients should be periodically
1425 reassessed to determine the need for maintenance treatment.

1426 **Discontinuation Strategy in Bipolar Disorder:** As with other AEDs, LAMICTAL
1427 should not be abruptly discontinued. In the controlled clinical trials, there was no increase in the
1428 incidence, type, or severity of adverse experiences following abrupt termination of LAMICTAL.
1429 In clinical trials in patients with bipolar disorder, 2 patients experienced seizures shortly after
1430 abrupt withdrawal of LAMICTAL. However, there were confounding factors that may have
1431 contributed to the occurrence of seizures in these bipolar patients. Discontinuation of
1432 LAMICTAL should involve a step-wise reduction of dose over at least 2 weeks (approximately
1433 50% per week) unless safety concerns require a more rapid withdrawal.

1434
1435 **Administration of LAMICTAL Chewable Dispersible Tablets:** LAMICTAL Chewable
1436 Dispersible Tablets may be swallowed whole, chewed, or dispersed in water or diluted fruit
1437 juice. If the tablets are chewed, consume a small amount of water or diluted fruit juice to aid in
1438 swallowing.

1439 To disperse LAMICTAL Chewable Dispersible Tablets, add the tablets to a small amount of
1440 liquid (1 teaspoon, or enough to cover the medication). Approximately 1 minute later, when the
1441 tablets are completely dispersed, swirl the solution and consume the entire quantity immediately.
1442 *No attempt should be made to administer partial quantities of the dispersed tablets.*

1443 HOW SUPPLIED

1444 LAMICTAL Tablets, 25-mg

1445 White, scored, shield-shaped tablets debossed with "LAMICTAL" and "25", bottles of 100
1446 (NDC 0173-0633-02).

1447 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled**
1448 **Room Temperature] in a dry place.**

1449 LAMICTAL Tablets, 100-mg

1450 Peach, scored, shield-shaped tablets debossed with "LAMICTAL" and "100", bottles of 100
1451 (NDC 0173-0642-55).

1452 LAMICTAL Tablets, 150-mg

1453 Cream, scored, shield-shaped tablets debossed with "LAMICTAL" and "150", bottles of 60
1454 (NDC 0173-0643-60).

1455 LAMICTAL Tablets, 200-mg

1456 Blue, scored, shield-shaped tablets debossed with "LAMICTAL" and "200", bottles of 60
1457 (NDC 0173-0644-60).

1458 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled**
1459 **Room Temperature] in a dry place and protect from light.**

1460

1461 LAMICTAL Chewable Dispersible Tablets, 2-mg

1462 White to off-white, round tablets debossed with “LTG” over “2”, bottles of 30 (NDC 0173-
1463 0699-00). ORDER DIRECTLY FROM GlaxoSmithKline 1-800-334-4153.

1464 **LAMICTAL Chewable Dispersible Tablets, 5-mg**

1465 White to off-white, caplet-shaped tablets debossed with “GX CL2”, bottles of 100 (NDC
1466 0173-0526-00).

1467 **LAMICTAL Chewable Dispersible Tablets, 25-mg**

1468 White, super elliptical-shaped tablets debossed with “GX CL5”, bottles of 100 (NDC 0173-
1469 0527-00).

1470 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled**
1471 **Room Temperature] in a dry place.**

1472

1473 **LAMICTAL Starter Kit for Patients Taking Valproate**

1474 **25-mg**, white, scored, shield-shaped tablets debossed with "LAMICTAL" and "25",
1475 blisterpack of 35 tablets (NDC 0173-0633-10).

1476 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled**
1477 **Room Temperature] in a dry place.**

1478

1479 **LAMICTAL Starter Kit for Patients Taking Carbamazepine, Phenytoin, Phenobarbital,**
1480 **Primidone, or Rifampin and Not Taking Valproate**

1481 **25-mg**, white, scored, shield-shaped tablets debossed with "LAMICTAL" and "25" and
1482 **100-mg**, peach, scored, shield-shaped tablets debossed with "LAMICTAL" and “100”,
1483 blisterpack of 84, 25-mg tablets and 14, 100-mg tablets (NDC 0173-0594-01)

1484 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled**
1485 **Room Temperature] in a dry place and protect from light.**

1486

1487 **LAMICTAL Starter Kit for Patients Not Taking Carbamazepine, Phenytoin,**
1488 **Phenobarbital, Primidone, Rifampin, or Valproate**

1489

1490 **25-mg**, white, scored, shield-shaped tablets debossed with "LAMICTAL" and "25" and
1491 **100-mg**, peach, scored, shield-shaped tablets debossed with "LAMICTAL" and “100”,
1492 blisterpack of 42, 25-mg tablets and 7, 100-mg tablets (NDC 0173-0594-02).

1493 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled**
1494 **Room Temperature] in a dry place and protect from light.**

1495 **PATIENT INFORMATION**

1496 The following wording is contained in a separate leaflet provided for patients.

1497

1498 **Information for the Patient**

1499

1500 **LAMICTAL[®] (lamotrigine) Tablets**

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LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

ALWAYS CHECK THAT YOU RECEIVE LAMICTAL

Patients prescribed LAMICTAL (lah-MICK-tall) have sometimes been given the wrong medicine in error because many medicines have names similar to LAMICTAL. Taking the wrong medication can cause serious health problems. When your healthcare provider gives you a prescription for LAMICTAL




- make sure you can read it clearly.
- talk to your pharmacist to check that you are given the correct medicine.
- check the tablets you receive against the pictures of the tablets below. The pictures 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.

LAMICTAL (lamotrigine) Tablets

 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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1516
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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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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.

Information About Your Medicine:

1528 The name of your medicine is LAMICTAL (lamotrigine). The decision to use LAMICTAL is
1529 one that you and your doctor should make together. When taking lamotrigine, it is important to
1530 follow your doctor's instructions.

1531

1532 ***1. The Purpose of Your Medicine:***

1533 ***For Patients With Epilepsy:*** LAMICTAL is intended to be used either alone or in
1534 combination with other medicines to treat seizures in people aged 2 years or older.

1535 ***For Patients With Bipolar Disorder:*** LAMICTAL is used as maintenance treatment of
1536 Bipolar I Disorder to delay the time to occurrence of mood episodes in people aged 18 years or
1537 older treated for acute mood episodes with standard therapy.

1538 If you are taking LAMICTAL to help prevent extreme mood swings, you may not experience
1539 the full effect for several weeks. Occasionally, the symptoms of depression or bipolar disorder
1540 may include thoughts of harming yourself or committing suicide. Tell your doctor immediately
1541 or go to the nearest hospital if you have any distressing thoughts or experiences during this initial
1542 period or at any other time. Also contact your doctor if you experience any worsening of your
1543 condition or develop other new symptoms at any time during your treatment.

1544 Some medicines used to treat depression have been associated with suicidal thoughts and
1545 suicidal behavior in children or teenagers. LAMICTAL is not approved for treating children or
1546 teenagers with mood disorders such as bipolar disorder or depression.

1547 ***2. Who Should Not Take LAMICTAL:***

1548 You should not take LAMICTAL if you had an allergic reaction to it in the past.

1549 ***3. Side Effects to Watch for:***

- 1550 • Most people who take LAMICTAL tolerate it well. Common side effects with LAMICTAL
1551 include dizziness, headache, blurred or double vision, lack of coordination, sleepiness,
1552 nausea, vomiting, insomnia, and rash. LAMICTAL may cause other side effects not listed in
1553 this leaflet. If you develop any side effects or symptoms you are concerned about or need
1554 more information, call your doctor.
- 1555 • Although most patients who develop rash while receiving LAMICTAL have mild to
1556 moderate symptoms, some individuals may develop a serious skin reaction that requires
1557 hospitalization. Rarely, deaths have been reported. These serious skin reactions are most
1558 likely to happen within the first 8 weeks of treatment with LAMICTAL. Serious skin
1559 reactions occur more often in children than in adults.
- 1560 • Rashes may be more likely to occur if you: (1) take LAMICTAL in combination with
1561 valproate [DEPAKENE[®] (valproic acid) or DEPAKOTE[®] (divalproex sodium)], (2) take a
1562 higher starting dose of LAMICTAL than your doctor prescribed, or (3) increase your dose of
1563 LAMICTAL faster than prescribed.
- 1564 • It is not possible to predict whether a mild rash will develop into a more serious reaction.
1565 **Therefore, if you experience a skin rash, hives, fever, swollen lymph glands, painful**
1566 **sores in the mouth or around the eyes, or swelling of lips or tongue, tell a doctor**

1567 **immediately, since these symptoms may be the first signs of a serious reaction. A doctor**
1568 **should evaluate your condition and decide if you should continue taking LAMICTAL.**

1569 ***4. The Use of LAMICTAL During Pregnancy and Breastfeeding:***

1570 The effects of LAMICTAL during pregnancy are not known at this time. If you are pregnant
1571 or are planning to become pregnant, talk to your doctor. Some LAMICTAL passes into breast
1572 milk and the effects of this on infants are unknown. Therefore, if you are breast-feeding, you
1573 should discuss this with your doctor to determine if you should continue to take LAMICTAL.

1574 ***5. Use of Birth Control Pills or Other Female Hormonal Products:***

- 1575 • Do not start or stop using birth control pills or other female hormonal products until you
1576 have consulted your doctor. Stopping or starting these products may-cause side effects
1577 (such as dizziness, lack of coordination, or double vision) or decrease the effectiveness
1578 of LAMICTAL.
- 1579 • Tell your doctor as soon as possible if you experience side effects or changes in your menstrual
1580 pattern (e.g., break-through bleeding) while taking LAMICTAL and birth control pills or
1581 other female hormonal products.

1582 ***6. How to Use LAMICTAL:***

- 1583 • It is important to take LAMICTAL exactly as instructed by your doctor. The dose of
1584 LAMICTAL must be increased slowly. It may take several weeks or months before your
1585 final dosage can be determined by your doctor, based on your response.
- 1586 • Do not increase your dose of LAMICTAL or take more frequent doses than those indicated
1587 by your doctor. Contact your doctor, if you stop taking LAMICTAL for any reason. Do not
1588 restart without consulting your doctor.
- 1589 • If you miss a dose of LAMICTAL, do not double your next dose.
- 1590 • Always tell your doctor and pharmacist if you are taking any other prescription or
1591 over-the-counter medicines. Tell your doctor before you start any other medicines.
- 1592 • Do NOT stop taking LAMICTAL or any of your other medicines unless instructed by your
1593 doctor.
- 1594 • Use caution before driving a car or operating complex, hazardous machinery until you know
1595 if LAMICTAL affects your ability to perform these tasks.
- 1596 • If you have epilepsy, tell your doctor if your seizures get worse or if you have any new types
1597 of seizures.

1598 ***7. How to Take LAMICTAL:***

1599 LAMICTAL Tablets should be swallowed whole. Chewing the tablets may leave a bitter taste.

1600 LAMICTAL Chewable Dispersible Tablets may be swallowed whole, chewed, or mixed in
1601 water or diluted fruit juice. If the tablets are chewed, consume a small amount of water or diluted
1602 fruit juice to aid in swallowing.

1603 To disperse LAMICTAL Chewable Dispersible Tablets, add the tablets to a small amount of
1604 liquid (1 teaspoon, or enough to cover the medication) in a glass or spoon. Approximately
1605 1 minute later, when the tablets are completely dispersed, mix the solution and take the entire
1606 amount immediately.

1607 **8. Storing Your Medicine:**
1608 Store LAMICTAL at room temperature away from heat and light. Always keep your
1609 medicines out of the reach of children.
1610 This medicine was prescribed for your use only to treat seizures or to treat Bipolar Disorder.
1611 Do not give the drug to others.
1612 If your doctor decides to stop your treatment, do not keep any leftover medicine unless your
1613 doctor tells you to. Throw away your medicine as instructed.
1614



1615
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1617 GlaxoSmithKline
1618 Research Triangle Park, NC 27709
1619 by DSM Pharmaceuticals, Inc.
1620 Greenville, NC 27834 or
1621 GlaxoSmithKline
1622 Research Triangle Park, NC 27709

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1627
1628 (Date of Issue) RL-

PHARMACIST--DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

1630 -----
1631
1632 **Information for the Patient**

1633
1634 **LAMICTAL[®] (lamotrigine) Tablets**
1635 **LAMICTAL[®] (lamotrigine) Chewable Dispersible Tablets**





1636
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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
---	---	---	--

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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1673 the full effect for several weeks. Occasionally, the symptoms of depression or bipolar disorder
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1675 or go to the nearest hospital if you have any distressing thoughts or experiences during this initial
1676 period or at any other time. Also contact your doctor if you experience any worsening of your
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1680 teenagers with mood disorders such as bipolar disorder or depression.

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1683 **3. Side Effects to Watch for:**

- 1684 • Most people who take LAMICTAL tolerate it well. Common side effects with
1685 LAMICTAL include dizziness, headache, blurred or double vision, lack of coordination,
1686 sleepiness, nausea, vomiting, insomnia, and rash. LAMICTAL may cause other side effects
1687 not listed in this leaflet. If you develop any side effects or symptoms you are concerned about
1688 or need more information, call your doctor.
- 1689 • Although most patients who develop rash while receiving LAMICTAL have mild to
1690 moderate symptoms, some individuals may develop a serious skin reaction that requires
1691 hospitalization. Rarely, deaths have been reported. These serious skin reactions are most
1692 likely to happen within the first 8 weeks of treatment with LAMICTAL. Serious skin
1693 reactions occur more often in children than in adults.
- 1694 • Rashes may be more likely to occur if you: (1) take LAMICTAL in combination with
1695 valproate [DEPAKENE[®] (valproic acid) or DEPAKOTE[®] (divalproex sodium)], (2) take a
1696 higher starting dose of LAMICTAL than your doctor prescribed, or (3) increase your dose of
1697 LAMICTAL faster than prescribed.
- 1698 • It is not possible to predict whether a mild rash will develop into a more serious reaction.
1699 **Therefore, if you experience a skin rash, hives, fever, swollen lymph glands, painful**
1700 **sores in the mouth or around the eyes, or swelling of lips or tongue, tell a doctor**
1701 **immediately, since these symptoms may be the first signs of a serious reaction. A doctor**
1702 **should evaluate your condition and decide if you should continue taking LAMICTAL.**

1703 **4. The Use of LAMICTAL During Pregnancy and Breastfeeding:**

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1705 or are planning to become pregnant, talk to your doctor. Some LAMICTAL passes into breast
1706 milk and the effects of this on infants are unknown. Therefore, if you are breastfeeding, you
1707 should discuss this with your doctor to determine if you should continue to take LAMICTAL.

1708 **5. Use of Birth Control Pills or Other Female Hormonal Products:**

- 1709 • Do not start or stop using birth control pills or other female hormonal products until you
1710 have consulted your doctor. Stopping or starting these products may cause side effects

1711 (such as dizziness, lack of coordination, or double vision) or to decrease the
1712 effectiveness of LAMICTAL.

1713
1714

- Tell your doctor as soon as possible if you experience side effects changes in your menstrual pattern (e.g., break-through bleeding) while taking LAMICTAL and birth control pills or other female hormonal products.

1718 **6. How to Use LAMICTAL:**

- It is important to take LAMICTAL exactly as instructed by your doctor. The dose of LAMICTAL must be increased slowly. It may take several weeks or months before your final dosage can be determined by your doctor, based on your response.
- Do not increase your dose of LAMICTAL or take more frequent doses than those indicated by your doctor. Contact your doctor, if you stop taking LAMICTAL for any reason. Do not restart without consulting your doctor.
- If you miss a dose of LAMICTAL, do not double your next dose.
- Always tell your doctor and pharmacist if you are taking any other prescription or over-the-counter medicines. Tell your doctor before you start any other medicines.
- Do NOT stop taking LAMICTAL or any of your other medicines unless instructed by your doctor.
- Use caution before driving a car or operating complex, hazardous machinery until you know if LAMICTAL affects your ability to perform these tasks.
- If you have epilepsy, tell your doctor if your seizures get worse or if you have any new types of seizures.

1734 **7. How to Take LAMICTAL:**

1735 LAMICTAL Tablets should be swallowed whole. Chewing the tablets may leave a bitter taste.
1736 LAMICTAL Chewable Dispersible Tablets may be swallowed whole, chewed, or mixed in
1737 water or diluted fruit juice. If the tablets are chewed, consume a small amount of water or diluted
1738 fruit juice to aid in swallowing.

1739 To disperse LAMICTAL Chewable Dispersible Tablets, add the tablets to a small amount of
1740 liquid (1 teaspoon, or enough to cover the medication) in a glass or spoon. Approximately
1741 1 minute later, when the tablets are completely dispersed, mix the solution and take the entire
1742 amount immediately.

1743 **8. Storing Your Medicine:**

1744 Store LAMICTAL at room temperature away from heat and light. Always keep your
1745 medicines out of the reach of children.

1746 This medicine was prescribed for your use only to treat seizures or to treat Bipolar Disorder.
1747 Do not give the drug to others.

1748 If your doctor decides to stop your treatment, do not keep any leftover medicine unless your
1749 doctor tells you to. Throw away your medicine as instructed.

1750



1751
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1757 GlaxoSmithKline
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