

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.

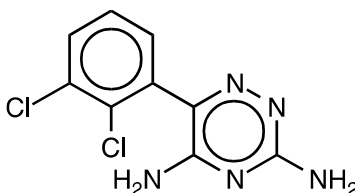
NEARLY ALL CASES OF LIFE-THREATENING RASHES ASSOCIATED WITH LAMICTAL HAVE OCCURRED WITHIN 2 TO 8 WEEKS OF TREATMENT INITIATION. HOWEVER, ISOLATED CASES HAVE BEEN REPORTED AFTER PROLONGED TREATMENT (E.G., 6 MONTHS). ACCORDINGLY, DURATION OF

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.**

49 **DESCRIPTION**

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



57
58
59 LAMICTAL Tablets are supplied for oral administration as 25-mg (white), 100-mg (peach),
60 150-mg (cream), and 200-mg (blue) tablets. Each tablet contains the labeled amount of
61 lamotrigine and the following inactive ingredients: lactose; magnesium stearate; microcrystalline
62 cellulose; povidone; sodium starch glycolate; FD&C Yellow No. 6 Lake (100-mg tablet only);
63 ferric oxide, yellow (150-mg tablet only); and FD&C Blue No. 2 Lake (200-mg tablet only).

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

69 **CLINICAL PHARMACOLOGY**

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

75 properties in the kindling model in rats both during kindling development and in the fully
76 kindled state. The relevance of these models to human epilepsy, however, is not known.

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

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

84 **Pharmacological Properties:** Although the relevance for human use is unknown, the
85 following data characterize the performance of LAMICTAL in receptor binding assays.
86 Lamotrigine had a weak inhibitory effect on the serotonin 5-HT₃ receptor (IC₅₀ = 18 μM). It does
87 not exhibit high affinity binding (IC₅₀>100 μM) to the following neurotransmitter receptors:
88 adenosine A₁ and A₂; adrenergic α₁, α₂, and β; dopamine D₁ and D₂; γ-aminobutyric acid
89 (GABA) A and B; histamine H₁; kappa opioid; muscarinic acetylcholine; and serotonin 5-HT₂.
90 Studies have failed to detect an effect of lamotrigine on dihydropyridine-sensitive calcium
91 channels. It had weak effects at sigma opioid receptors (IC₅₀ = 145 μM). Lamotrigine did not
92 inhibit the uptake of norepinephrine, dopamine, or serotonin, (IC₅₀>200 μM) when tested in rat
93 synaptosomes and/or human platelets in vitro.

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

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

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

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

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

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

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

126

127 **Table 1. Mean* Pharmacokinetic Parameters in Healthy Volunteers and Adult Patients**
 128 **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)

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

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

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

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

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

155 concentrations of phenytoin, phenobarbital, or valproate. Lamotrigine did not displace other
156 AEDs (carbamazepine, phenytoin, phenobarbital) from protein binding sites.

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

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

167 Carbamazepine, phenytoin, phenobarbital, and primidone have been shown to increase the
168 apparent clearance of lamotrigine (see DOSAGE AND ADMINISTRATION and
169 PRECAUTIONS: Drug Interactions). Most clinical experience is derived from patients taking
170 these AEDs.

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

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

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

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

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

192 The pharmacokinetics of LAMICTAL were not changed by coadministration of bupropion
193 (see PRECAUTIONS: Drug Interactions).

194 Coadministration of olanzapine did not have a clinically relevant effect on LAMICTAL
195 pharmacokinetics (see PRECAUTIONS: Drug Interactions).

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

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

204 **Dose Proportionality:** In healthy volunteers not receiving any other medications and given
205 single doses, the plasma concentrations of lamotrigine increased in direct proportion to the dose
206 administered over the range of 50 to 400 mg. In 2 small studies (n = 7 and 8) of patients with
207 epilepsy who were maintained on other AEDs, there also was a linear relationship between dose
208 and lamotrigine plasma concentrations at steady state following doses of 50 to 350 mg twice
209 daily.

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

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

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

231 **Age: Pediatric Patients:** The pharmacokinetics of LAMICTAL following a single
232 2-mg/kg dose were evaluated in 2 studies of pediatric patients (n = 29 for patients aged
233 10 months to 5.9 years and n = 26 for patients aged 5 to 11 years). Forty-three patients received

234 concomitant therapy with other AEDs and 12 patients received LAMICTAL as monotherapy.
 235 Lamotrigine pharmacokinetic parameters for pediatric patients are summarized in Table 2.

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

248
 249 **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,	11	‡	‡	1.3

phenytoin, phenobarbital, or primidone*				
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone* plus valproate	8	‡	‡	0.5
Patients taking valproate only	4	‡	‡	0.3

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

254 † Two subjects were included in the calculation for mean T_{max} .

255 ‡ Parameter not estimated.

256

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

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

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

268 CLINICAL STUDIES

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

275 **Monotherapy With LAMICTAL in Adults With Partial Seizures Already Receiving** 276 **Treatment With Carbamazepine, Phenytoin, Phenobarbital, or Primidone as the**

277 **Single AED:** The effectiveness of monotherapy with LAMICTAL was established in a
278 multicenter, double-blind clinical trial enrolling 156 adult outpatients with partial seizures. The
279 patients experienced at least 4 simple partial, complex partial, and/or secondarily generalized
280 seizures during each of 2 consecutive 4-week periods while receiving carbamazepine or
281 phenytoin monotherapy during baseline. LAMICTAL (target dose of 500 mg/day) or valproate
282 (1,000 mg/day) was added to either carbamazepine or phenytoin monotherapy over a 4-week

283 period. Patients were then converted to monotherapy with LAMICTAL or valproate during the
284 next 4 weeks, then continued on monotherapy for an additional 12-week period.

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

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

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

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

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

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

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

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

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

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

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

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

362 tonic-clonic seizures (36% reduction versus 10% increase for LAMICTAL and placebo,
363 respectively).

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

374 The primary efficacy endpoint was percentage change from baseline in primary generalized
375 tonic-clonic seizures. For the intent-to-treat population, the median percent reduction of primary
376 generalized tonic-clonic seizures was 66% in patients treated with LAMICTAL and 34% on
377 placebo, a difference that was statistically significant (p=0.006).

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

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

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

402 In Study 2, patients received double-blind monotherapy with LAMICTAL (100 to
403 400 mg/day, n = 59), or placebo (n = 70). LAMICTAL was superior to placebo in delaying time
404 to occurrence of a mood episode. The mean LAMICTAL dose was about 211 mg/day.

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

409 INDICATIONS AND USAGE

410 Epilepsy:

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

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

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

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

425 The effectiveness of LAMICTAL as maintenance treatment was established in
426 2 placebo-controlled trials of 18 months' duration in patients with Bipolar I Disorder as defined
427 by DSM-IV (see CLINICAL STUDIES: Bipolar Disorder). The physician who elects to use
428 LAMICTAL for periods extending beyond 18 months should periodically re-evaluate the
429 long-term usefulness of the drug for the individual patient.

430 CONTRAINDICATIONS

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

433 WARNINGS

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

436 **ALTHOUGH BENIGN RASHES ALSO OCCUR WITH LAMICTAL, IT IS NOT**
437 **POSSIBLE TO PREDICT RELIABLY WHICH RASHES WILL PROVE TO BE**
438 **SERIOUS OR LIFE THREATENING. ACCORDINGLY, LAMICTAL SHOULD**
439 **ORDINARILY BE DISCONTINUED AT THE FIRST SIGN OF RASH, UNLESS THE**

440 **RASH IS CLEARLY NOT DRUG RELATED. DISCONTINUATION OF TREATMENT**
441 **MAY NOT PREVENT A RASH FROM BECOMING LIFE THREATENING OR**
442 **PERMANENTLY DISABLING OR DISFIGURING.**

443 **Serious Rash: Pediatric Population:** The incidence of serious rash associated with
444 hospitalization and discontinuation of LAMICTAL in a prospectively followed cohort of
445 pediatric patients with epilepsy receiving adjunctive therapy was approximately 0.8% (16 of
446 1,983). When 14 of these cases were reviewed by 3 expert dermatologists, there was
447 considerable disagreement as to their proper classification. To illustrate, one dermatologist
448 considered none of the cases to be Stevens-Johnson syndrome; another assigned 7 of the 14 to
449 this diagnosis. There was 1 rash-related death in this 1,983 patient cohort. Additionally, there
450 have been rare cases of toxic epidermal necrolysis with and without permanent sequelae and/or
451 death in US and foreign postmarketing experience.

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

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

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

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

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

476
477 **Hypersensitivity Reactions:** Hypersensitivity reactions, some fatal or life threatening, have
478 also occurred. Some of these reactions have included clinical features of multiorgan
479 failure/dysfunction, including hepatic abnormalities and evidence of disseminated intravascular

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

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

488

489

490 **Acute Multiorgan Failure:** Multiorgan failure, which in some cases has been fatal or
491 irreversible, has been observed in patients receiving LAMICTAL. Fatalities associated with
492 multiorgan failure and various degrees of hepatic failure have been reported in 2 of 3,796 adult
493 patients and 4 of 2,435 pediatric patients who received LAMICTAL in clinical trials. No such
494 fatalities have been reported in bipolar patients in clinical trials. Rare fatalities from multiorgan
495 failure have also been reported in compassionate use and postmarketing use. The majority of
496 these deaths occurred in association with other serious medical events, including status
497 epilepticus and overwhelming sepsis, and hantavirus making it difficult to identify the initial
498 cause.

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

506

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

511 **Suicidal Behavior and Ideation:** Antiepileptic drugs (AEDs), including LAMICTAL,
512 increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication.
513 Patients treated with any AED for any indication should be monitored for the emergence or
514 worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or
515 behavior.

516 Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy)
517 of 11 different AEDs showed that patients randomized to one of the AEDs had approximately
518 twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior
519 compared to patients randomized to placebo. In these trials, which had a median treatment

520 duration of 12 weeks, the estimated incidence of suicidal behavior or ideation among 27,863
 521 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients,
 522 representing an increase of approximately 1 case of suicidal thinking or behavior for every 530
 523 patients treated. There were 4 suicides in drug-treated patients in the trials and none in placebo-
 524 treated patients, but the number of events is too small to allow any conclusion about drug effect
 525 on suicide.

526 The increased risk of suicidal thoughts or behavior with AEDs was observed as early as
 527 1 week after starting treatment with AEDs and persisted for the duration of treatment assessed.
 528 Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal
 529 thoughts or behavior beyond 24 weeks could not be assessed.

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

534 Table 3 shows absolute and relative risk by indication for all evaluated AEDs.
 535
 536

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

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

537
 538 The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy
 539 than in clinical trials for psychiatric or other conditions, but the absolute risk differences were
 540 similar for the epilepsy and psychiatric indications.

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

547 Patients, their caregivers, and families should be informed that AEDs increase the risk of
 548 suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or
 549 worsening of the signs and symptoms of depression, any unusual changes in mood or behavior,

550 or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of
551 concern should be reported immediately to healthcare providers.

552
553 **Withdrawal Seizures:** As with other AEDs, LAMICTAL should not be abruptly discontinued.
554 In patients with epilepsy there is a possibility of increasing seizure frequency. In clinical trials in
555 patients with Bipolar Disorder, 2 patients experienced seizures shortly after abrupt withdrawal of
556 LAMICTAL. However, there were confounding factors that may have contributed to the
557 occurrence of seizures in these bipolar patients. Unless safety concerns require a more rapid
558 withdrawal, the dose of LAMICTAL should be tapered over a period of at least 2 weeks (see
559 DOSAGE AND ADMINISTRATION).

560 **PRECAUTIONS**

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

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

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

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

587 **ACCORDINGLY, LAMICTAL SHOULD ORDINARILY BE DISCONTINUED AT THE**
588 **FIRST SIGN OF RASH, UNLESS THE RASH IS CLEARLY NOT DRUG RELATED.**

589 **DISCONTINUATION OF TREATMENT MAY NOT PREVENT A RASH FROM**
590 **BECOMING LIFE THREATENING OR PERMANENTLY DISABLING OR**
591 **DISFIGURING.**

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

602 **Use in Patients With Epilepsy:**

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

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

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

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

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

629 **Children and Adolescents (less than 18 years of age):** Treatment with
630 antidepressants is associated with an increased risk of suicidal thinking and behavior in children
631 and adolescents with major depressive disorder and other psychiatric disorders. It is not known
632 whether LAMICTAL is associated with a similar risk in this population (see WARNINGS:
633 Suicidal Behavior and Ideation and PRECAUTIONS: Clinical Worsening and Suicide Risk
634 Associated With Bipolar Disorder).

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

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

638 Patients with bipolar disorder may experience worsening of their depressive symptoms and/or
639 the emergence of suicidal ideation and behaviors (suicidality) whether or not they are taking
640 medications for bipolar disorder. Patients should be closely monitored for clinical worsening
641 (including development of new symptoms) and suicidality, especially at the beginning of a
642 course of treatment, or at the time of dose changes (also see WARNINGS: Suicidal Behavior
643 and Ideation).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

703 Patients should be advised to notify their physicians if they become pregnant or intend to
704 become pregnant during therapy. Patients should be advised to notify their physicians if they
705 intend to breast-feed or are breastfeeding an infant.

706 Patients should also be encouraged to enroll in the North American Antiepileptic Drug
707 (NAAED) Pregnancy Registry if they become pregnant. This registry is collecting information

708 about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll-free
709 number 1-888-233-2334 (see PRECAUTIONS: Pregnancy).

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

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

720 Patients should be informed of the availability of a Medication Guide, and they should be
721 instructed to read the Medication Guide prior to taking LAMICTAL. Patients should be
722 instructed to take LAMICTAL only as prescribed. See PATIENT INFORMATION at the end of
723 this labeling for the text of the Medication Guide provided for patients.

724 **Laboratory Tests:** The value of monitoring plasma concentrations of LAMICTAL has not
725 been established. Because of the possible pharmacokinetic interactions between LAMICTAL
726 and other drugs including AEDs (see Table 4), monitoring of the plasma levels of LAMICTAL
727 and concomitant drugs may be indicated, particularly during dosage adjustments. In general,
728 clinical judgment should be exercised regarding monitoring of plasma levels of LAMICTAL and
729 other drugs and whether or not dosage adjustments are necessary.

730 **Drug Interactions:**

731 The net effects of drug interactions with LAMICTAL are summarized in Table 4 (see also
732 DOSAGE AND ADMINISTRATION).

733 **Oral Contraceptives:** In 16 female volunteers, an oral contraceptive preparation containing
734 30 mcg ethinylestradiol and 150 mcg levonorgestrel increased the apparent clearance of
735 lamotrigine (300 mg/day) by approximately 2-fold with a mean decrease in AUC of 52% and in
736 C_{max} of 39%. In this study, trough serum lamotrigine concentrations gradually increased and
737 were approximately 2-fold higher on average at the end of the week of the inactive hormone
738 preparation compared to trough lamotrigine concentrations at the end of the active hormone
739 cycle.

740 Gradual transient increases in lamotrigine plasma levels (approximate 2-fold increase)
741 occurred during the week of inactive hormone preparation (“pill-free” week) for women not also
742 taking a drug that increased the clearance of lamotrigine (carbamazepine, phenytoin,
743 phenobarbital, primidone, or rifampin). The increase in lamotrigine plasma levels will be greater
744 if the dose of LAMICTAL is increased in the few days before or during the “pill-free” week.
745 Increases in lamotrigine plasma levels could result in dose-dependent adverse effects (see
746 PRECAUTIONS: Concomitant Use With Oral Contraceptives).

747 In the same study, coadministration of LAMICTAL (300 mg/day) in 16 female volunteers did
748 not affect the pharmacokinetics of the ethinylestradiol component of the oral contraceptive
749 preparation. There was a mean decrease in the AUC and C_{max} of the levonorgestrel component of
750 19% and 12%, respectively. Measurement of serum progesterone indicated that there was no
751 hormonal evidence of ovulation in any of the 16 volunteers, although measurement of serum
752 FSH, LH, and estradiol indicated that there was some loss of suppression of the hypothalamic-
753 pituitary-ovarian axis.

754 The effects of doses of LAMICTAL other than 300 mg/day have not been systematically
755 evaluated in controlled clinical trials.

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

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

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

769 **Bupropion:** The pharmacokinetics of a 100-mg single dose of LAMICTAL in healthy
770 volunteers (n = 12) were not changed by coadministration of bupropion sustained-release
771 formulation (150 mg twice a day) starting 11 days before LAMICTAL.

772 **Carbamazepine:** LAMICTAL has no appreciable effect on steady-state carbamazepine
773 plasma concentration. Limited clinical data suggest there is a higher incidence of dizziness,
774 diplopia, ataxia, and blurred vision in patients receiving carbamazepine with LAMICTAL than in
775 patients receiving other AEDs with LAMICTAL (see ADVERSE REACTIONS). The
776 mechanism of this interaction is unclear. The effect of LAMICTAL on plasma concentrations of
777 carbamazepine-epoxide is unclear. In a small subset of patients (n = 7) studied in a
778 placebo-controlled trial, LAMICTAL had no effect on carbamazepine-epoxide plasma
779 concentrations, but in a small, uncontrolled study (n = 9), carbamazepine-epoxide levels
780 increased.

781 The addition of carbamazepine decreases lamotrigine steady-state concentrations by
782 approximately 40%.

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

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

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

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

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

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

801 In the same study, the AUC and C_{max} of lamotrigine was reduced on average by 24% and
802 20%, respectively, following the addition of olanzapine to LAMICTAL in healthy male
803 volunteers compared to those receiving LAMICTAL alone. This reduction in lamotrigine plasma
804 concentrations is not expected to be clinically relevant.

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

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

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

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

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

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

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

827 **Valproate:** When LAMICTAL was administered to healthy volunteers (n = 18) receiving
 828 valproate, the trough steady-state valproate plasma concentrations decreased by an average of
 829 25% over a 3-week period, and then stabilized. However, adding LAMICTAL to the existing
 830 therapy did not cause a change in valproate plasma concentrations in either adult or pediatric
 831 patients in controlled clinical trials.

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

836 **Zonisamide:** In a study of 18 patients with epilepsy, coadministration of zonisamide (200 to
 837 400 mg/day) with LAMICTAL (150 to 500 mg/day) for 35 days had no significant effect on the
 838 pharmacokinetics of lamotrigine.

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

844 **Other:** Results of in vitro experiments suggest that clearance of lamotrigine is unlikely to be
 845 reduced by concomitant administration of amitriptyline, clonazepam, clozapine, fluoxetine,
 846 haloperidol, lorazepam, phenelzine, risperidone, sertraline, or trazodone (see CLINICAL
 847 PHARMACOLOGY: Pharmacokinetics and Drug Metabolism).

848 Results of in vitro experiments suggest that lamotrigine does not reduce the clearance of drugs
 849 eliminated predominantly by CYP2D6 (see CLINICAL PHARMACOLOGY).

850

851 **Table 4. 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	↔

852 * From adjunctive clinical trials and volunteer studies.

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

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

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

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

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

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

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

865 ↔ = No significant effect.

866 ? = Conflicting data.

867

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

869 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** No evidence of carcinogenicity
870 was seen in 1 mouse study or 2 rat studies following oral administration of lamotrigine for up to
871 2 years at maximum tolerated doses (30 mg/kg per day for mice and 10 to 15 mg/kg per day for
872 rats, doses that are equivalent to 90 mg/m² and 60 to 90 mg/m², respectively). Steady-state
873 plasma concentrations ranged from 1 to 4 mcg/mL in the mouse study and 1 to 10 mcg/mL in the
874 rat study. Plasma concentrations associated with the recommended human doses of 300 to
875 500 mg/day are generally in the range of 2 to 5 mcg/mL, but concentrations as high as
876 19 mcg/mL have been recorded.

877 Lamotrigine was not mutagenic in the presence or absence of metabolic activation when
878 tested in 2 gene mutation assays (the Ames test and the in vitro mammalian mouse lymphoma
879 assay). In 2 cytogenetic assays (the in vitro human lymphocyte assay and the in vivo rat bone

880 marrow assay), lamotrigine did not increase the incidence of structural or numerical
881 chromosomal abnormalities.

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

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

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

901 Lamotrigine did not affect fertility, teratogenesis, or postnatal development when rats were
902 dosed prior to and during mating, and throughout gestation and lactation at doses equivalent to
903 0.4 times the highest usual human maintenance dose on a mg/m² basis.

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

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

918 **Non-Teratogenic Effects:** As with other antiepileptic drugs, physiological changes during
919 pregnancy may affect lamotrigine concentrations and/or therapeutic effect. There have been

920 reports of decreased lamotrigine concentrations during pregnancy and restoration of pre-partum
921 concentrations after delivery. Dosage adjustments may be necessary to maintain clinical
922 response.

923 **Pregnancy Exposure Registry:** To provide information regarding the effects of in utero
924 exposure to LAMICTAL, physicians are advised to recommend that pregnant patients taking
925 LAMICTAL enroll in the NAAED Pregnancy Registry. This can be done by calling the toll free
926 number 1-888-233-2334, and must be done by patients themselves. Information on the registry
927 can also be found at the website <http://www.aedpregnancyregistry.org/>.

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

932
933 **Labor and Delivery:** The effect of LAMICTAL on labor and delivery in humans is unknown.

934 **Use in Nursing Mothers:** Preliminary data indicate that lamotrigine passes into human milk.
935 Because the effects on the infant exposed to LAMICTAL by this route are unknown,
936 breastfeeding while taking LAMICTAL is not recommended.

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

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

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

947 **ADVERSE REACTIONS**

948 **SERIOUS RASH REQUIRING HOSPITALIZATION AND DISCONTINUATION OF**
949 **LAMICTAL, INCLUDING STEVENS-JOHNSON SYNDROME AND TOXIC**
950 **EPIDERMAL NECROLYSIS, HAVE OCCURRED IN ASSOCIATION WITH**
951 **THERAPY WITH LAMICTAL. RARE DEATHS HAVE BEEN REPORTED, BUT**
952 **THEIR NUMBERS ARE TOO FEW TO PERMIT A PRECISE ESTIMATE OF THE**
953 **RATE (see BOX WARNING).**

954 **Epilepsy:**

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

959 diplopia, blurred vision, nausea, vomiting, and rash. Dizziness, diplopia, ataxia, blurred vision,
960 nausea, and vomiting were dose related. Dizziness, diplopia, ataxia, and blurred vision occurred
961 more commonly in patients receiving carbamazepine with LAMICTAL than in patients receiving
962 other AEDs with LAMICTAL. Clinical data suggest a higher incidence of rash, including serious
963 rash, in patients receiving concomitant valproate than in patients not receiving valproate (see
964 WARNINGS).

965 Approximately 11% of the 3,378 adult patients who received LAMICTAL as adjunctive
966 therapy in premarketing clinical trials discontinued treatment because of an adverse experience.
967 The adverse events most commonly associated with discontinuation were rash (3.0%), dizziness
968 (2.8%), and headache (2.5%).

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

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

981 Approximately 10% of the 420 adult patients who received LAMICTAL as monotherapy in
982 premarketing clinical trials discontinued treatment because of an adverse experience. The
983 adverse events most commonly associated with discontinuation were rash (4.5%), headache
984 (3.1%), and asthenia (2.4%).

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

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

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

999 ***Incidence in Controlled Clinical Studies of Epilepsy:*** The prescriber should be aware
1000 that the figures in Tables 5, 6, 7, and 8 cannot be used to predict the frequency of adverse
1001 experiences in the course of usual medical practice where patient characteristics and other factors
1002 may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot
1003 be directly compared with figures obtained from other clinical investigations involving different
1004 treatments, uses, or investigators. An inspection of these frequencies, however, does provide the
1005 prescriber with one basis to estimate the relative contribution of drug and nondrug factors to the
1006 adverse event incidences in the population studied.

1007 ***Incidence in Controlled Adjunctive Clinical Studies in Adults With Epilepsy:***
1008 Table 5 lists treatment-emergent signs and symptoms that occurred in at least 2% of adult
1009 patients with epilepsy treated with LAMICTAL in placebo-controlled trials and were
1010 numerically more common in the patients treated with LAMICTAL. In these studies, either
1011 LAMICTAL or placebo was added to the patient's current AED therapy. Adverse events were
1012 usually mild to moderate in intensity.

1013 **Table 5. Treatment-Emergent Adverse Event Incidence in Placebo-Controlled Adjunctive**
 1014 **Trials in Adult Patients With Epilepsy* (Events in at least 2% of patients treated with**
 1015 **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

1016 * Patients in these adjunctive studies were receiving 1 to 3 of the following concomitant AEDs
1017 (carbamazepine, phenytoin, phenobarbital, or primidone) in addition to LAMICTAL or
1018 placebo. Patients may have reported multiple adverse experiences during the study or at
1019 discontinuation; thus, patients may be included in more than one category.

1020 † Adverse experiences reported by at least 2% of patients treated with LAMICTAL are
1021 included.

1022
1023 In a randomized, parallel study comparing placebo and 300 and 500 mg/day of LAMICTAL,
1024 some of the more common drug-related adverse events were dose related (see Table 6).

1025

1026 **Table 6. Dose-Related Adverse Events From a Randomized, Placebo-Controlled Trial in**
 1027 **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*

1028 *Significantly greater than placebo group (p<0.05).

1029 †Significantly greater than group receiving LAMICTAL 300 mg (p<0.05).

1030

1031 Other events that occurred in more than 1% of patients but equally or more frequently in the
 1032 placebo group included: asthenia, back pain, chest pain, flatulence, menstrual disorder, myalgia,
 1033 paresthesia, respiratory disorder, and urinary tract infection.

1034 The overall adverse experience profile for LAMICTAL was similar between females and
 1035 males, and was independent of age. Because the largest non-Caucasian racial subgroup was only
 1036 6% of patients exposed to LAMICTAL in placebo-controlled trials, there are insufficient data to
 1037 support a statement regarding the distribution of adverse experience reports by race. Generally,
 1038 females receiving either adjunctive LAMICTAL or placebo were more likely to report adverse
 1039 experiences than males. The only adverse experience for which the reports on LAMICTAL were
 1040 greater than 10% more frequent in females than males (without a corresponding difference by
 1041 gender on placebo) was dizziness (difference = 16.5%). There was little difference between
 1042 females and males in the rates of discontinuation of LAMICTAL for individual adverse
 1043 experiences.

1044 ***Incidence in a Controlled Monotherapy Trial in Adults With Partial Seizures:***

1045 Table 7 lists treatment-emergent signs and symptoms that occurred in at least 5% of patients with
 1046 epilepsy treated with monotherapy with LAMICTAL in a double-blind trial following
 1047 discontinuation of either concomitant carbamazepine or phenytoin not seen at an equivalent
 1048 frequency in the control group.

1049

1050 **Table 7. Treatment-Emergent Adverse Event Incidence in Adults With Partial Seizures in**
 1051 **a Controlled Monotherapy Trial* (Events in at least 5% of patients treated with**
 1052 **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

1053 * Patients in these studies were converted to LAMICTAL or valproate monotherapy from
 1054 adjunctive therapy with carbamazepine or phenytoin. Patients may have reported multiple
 1055 adverse experiences during the study; thus, patients may be included in more than one
 1056 category.

1057 [†] Adverse experiences reported by at least 5% of patients are included.

1058 [‡] Up to 500 mg/day.

1059 [§] 1,000 mg/day.

1060
 1061 Adverse events that occurred with a frequency of less than 5% and greater than 2% of patients
 1062 receiving LAMICTAL and numerically more frequent than placebo were:

1063 **Body as a Whole:** Asthenia, fever.
 1064 **Digestive:** Anorexia, dry mouth, rectal hemorrhage, peptic ulcer.
 1065 **Metabolic and Nutritional:** Peripheral edema.
 1066 **Nervous System:** Amnesia, ataxia, depression, hypesthesia, libido increase, decreased
 1067 reflexes, increased reflexes, nystagmus, irritability,.
 1068 **Respiratory:** Epistaxis, bronchitis, dyspnea.
 1069 **Skin and Appendages:** Contact dermatitis, dry skin, sweating.
 1070 **Special Senses:** Vision abnormality.

1071 **Incidence in Controlled Adjunctive Trials in Pediatric Patients With Epilepsy:**
 1072 Table 8 lists adverse events that occurred in at least 2% of 339 pediatric patients with partial
 1073 seizures or generalized seizures of Lennox-Gastaut syndrome, who received LAMICTAL up to
 1074 15 mg/kg per day or a maximum of 750 mg per day. Reported adverse events were classified
 1075 using COSTART terminology.

1076
 1077 **Table 8. Treatment-Emergent Adverse Event Incidence in Placebo-Controlled Adjunctive**
 1078 **Trials in Pediatric Patients With Epilepsy (Events in at least 2% of patients treated with**
 1079 **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

1080

1081 **Bipolar Disorder:** The most commonly observed ($\geq 5\%$) adverse experiences seen in
1082 association with the use of LAMICTAL as monotherapy (100 to 400 mg/day) in Bipolar
1083 Disorder in the 2 double-blind, placebo-controlled trials of 18 months' duration, and numerically
1084 more frequent than in placebo-treated patients are included in Table 9. Adverse events that
1085 occurred in at least 5% of patients and were numerically more common during the dose
1086 escalation phase of LAMICTAL in these trials (when patients may have been receiving
1087 concomitant medications) compared to the monotherapy phase were: headache (25%), rash
1088 (11%), dizziness (10%), diarrhea (8%), dream abnormality (6%), and pruritus (6%).

1089 During the monotherapy phase of the double-blind, placebo-controlled trials of 18 months'
1090 duration, 13% of 227 patients who received LAMICTAL (100 to 400 mg/day), 16% of
1091 190 patients who received placebo, and 23% of 166 patients who received lithium discontinued
1092 therapy because of an adverse experience. The adverse events which most commonly led to
1093 discontinuation of LAMICTAL were rash (3%) and mania/hypomania/mixed mood adverse
1094 events (2%). Approximately 16% of 2,401 patients who received LAMICTAL (50 to
1095 500 mg/day) for Bipolar Disorder in premarketing trials discontinued therapy because of an
1096 adverse experience; most commonly due to rash (5%) and mania/hypomania/mixed mood
1097 adverse events (2%).

1098 ***Incidence in Controlled Clinical Studies of LAMICTAL for the Maintenance***
1099 ***Treatment of Bipolar I Disorder:*** Table 9 lists treatment-emergent signs and symptoms that
1100 occurred in at least 5% of patients with Bipolar Disorder treated with LAMICTAL monotherapy
1101 (100 to 400 mg/day), following the discontinuation of other psychotropic drugs, in
1102 2 double-blind, placebo-controlled trials of 18 months' duration and were numerically more
1103 frequent than in the placebo group.

1104

1105 **Table 9. Treatment-Emergent Adverse Event Incidence in 2 Placebo-Controlled Trials in**
 1106 **Adults With Bipolar I Disorder* (Events in at least 5% of patients treated with**
 1107 **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

1108 * Patients in these studies were converted to LAMICTAL (100 to 400 mg/day) or placebo
 1109 monotherapy from add-on therapy with other psychotropic medications. Patients may have
 1110 reported multiple adverse experiences during the study; thus, patients may be included in
 1111 more than one category.

1112 † Adverse experiences reported by at least 5% of patients are included.

1113 ‡ In the overall bipolar and other mood disorders clinical trials, the rate of serious rash was
 1114 0.08% (1 of 1,233) of adult patients who received LAMICTAL as initial monotherapy and
 1115 0.13% (2 of 1,538) of adult patients who received LAMICTAL as adjunctive therapy (see
 1116 WARNINGS).

1117
 1118 These adverse events were usually mild to moderate in intensity.
 1119 Other events that occurred in 5% or more patients but equally or more frequently in the
 1120 placebo group included: dizziness, mania, headache, infection, influenza, pain, accidental injury,
 1121 diarrhea, and dyspepsia.

1122 Adverse events that occurred with a frequency of less than 5% and greater than 1% of patients
 1123 receiving LAMICTAL and numerically more frequent than placebo were:

1124 **General:** Fever, neck pain.
1125 **Cardiovascular:** Migraine.
1126 **Digestive:** Flatulence.
1127 **Metabolic and Nutritional:** Weight gain, edema.
1128 **Musculoskeletal:** Arthralgia, myalgia.
1129 **Nervous System:** Amnesia, depression, agitation, emotional lability, dyspraxia, abnormal
1130 thoughts, dream abnormality, hypoesthesia.
1131 **Respiratory:** Sinusitis.
1132 **Urogenital:** Urinary frequency.
1133 **Adverse Events Following Abrupt Discontinuation:** In the 2 maintenance trials, there
1134 was no increase in the incidence, severity or type of adverse events in Bipolar Disorder patients
1135 after abruptly terminating LAMICTAL therapy. In clinical trials in patients with Bipolar
1136 Disorder, 2 patients experienced seizures shortly after abrupt withdrawal of LAMICTAL.
1137 However, there were confounding factors that may have contributed to the occurrence of seizures
1138 in these bipolar patients (see DOSAGE AND ADMINISTRATION).
1139 **Mania/Hypomania/Mixed Episodes:** During the double-blind, placebo-controlled clinical
1140 trials in Bipolar I Disorder in which patients were converted to LAMICTAL monotherapy (100
1141 to 400 mg/day) from other psychotropic medications and followed for durations up to 18 months,
1142 the rate of manic or hypomanic or mixed mood episodes reported as adverse experiences was 5%
1143 for patients treated with LAMICTAL (n = 227), 4% for patients treated with lithium (n = 166),
1144 and 7% for patients treated with placebo (n = 190). In all bipolar controlled trials combined,
1145 adverse events of mania (including hypomania and mixed mood episodes) were reported in 5%
1146 of patients treated with LAMICTAL (n = 956), 3% of patients treated with lithium (n = 280), and
1147 4% of patients treated with placebo (n = 803).
1148 The overall adverse event profile for LAMICTAL was similar between females and males,
1149 between elderly and nonelderly patients, and among racial groups.
1150 **Other Adverse Events Observed During All Clinical Trials For Pediatric and Adult**
1151 **Patients With Epilepsy or Bipolar Disorder and Other Mood Disorders:** LAMICTAL
1152 has been administered to 6,694 individuals for whom complete adverse event data was captured
1153 during all clinical trials, only some of which were placebo controlled. During these trials, all
1154 adverse events were recorded by the clinical investigators using terminology of their own
1155 choosing. To provide a meaningful estimate of the proportion of individuals having adverse
1156 events, similar types of events were grouped into a smaller number of standardized categories
1157 using modified COSTART dictionary terminology. The frequencies presented represent the
1158 proportion of the 6,694 individuals exposed to LAMICTAL who experienced an event of the
1159 type cited on at least one occasion while receiving LAMICTAL. All reported events are included
1160 except those already listed in the previous tables or elsewhere in the labeling, those too general
1161 to be informative, and those not reasonably associated with the use of the drug.
1162 Events are further classified within body system categories and enumerated in order of
1163 decreasing frequency using the following definitions: *frequent* adverse events are defined as

1164 those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100
1165 to 1/1,000 patients; *rare* adverse events are those occurring in fewer than 1/1,000 patients.

1166 **Body as a Whole: Infrequent:** Allergic reaction, chills, halitosis, and malaise. **Rare:**
1167 Abdomen enlarged, abscess, and suicide/suicide attempt.

1168 **Cardiovascular System: Infrequent:** Flushing, hot flashes, hypertension, palpitations,
1169 postural hypotension, syncope, tachycardia, and vasodilation. **Rare:** Angina pectoris, atrial
1170 fibrillation, deep thrombophlebitis, ECG abnormality, and myocardial infarction.

1171 **Dermatological: Infrequent:** Acne, alopecia, hirsutism, maculopapular rash, skin
1172 discoloration, and urticaria. **Rare:** Angioedema, erythema, exfoliative dermatitis, fungal
1173 dermatitis, herpes zoster, leukoderma, multiforme erythema, petechial rash, pustular rash,
1174 seborrhea, Stevens-Johnson syndrome, and vesiculobullous rash.

1175 **Digestive System: Infrequent:** Dysphagia, eructation, gastritis, gingivitis, increased
1176 appetite, increased salivation, liver function tests abnormal, and mouth ulceration. **Rare:**
1177 Gastrointestinal hemorrhage, glossitis, gum hemorrhage, gum hyperplasia, hematemesis,
1178 hemorrhagic colitis, hepatitis, melena, stomach ulcer, stomatitis, thirst, and tongue edema.

1179 **Endocrine System: Rare:** Goiter and hypothyroidism.

1180 **Hematologic and Lymphatic System: Infrequent:** Ecchymosis and leukopenia. **Rare:**
1181 Anemia, eosinophilia, fibrin decrease, fibrinogen decrease, iron deficiency anemia, leukocytosis,
1182 lymphocytosis, macrocytic anemia, petechia, and thrombocytopenia.

1183 **Metabolic and Nutritional Disorders: Infrequent:** Aspartate transaminase increased.
1184 **Rare:** Alcohol intolerance, alkaline phosphatase increase, alanine transaminase increase,
1185 bilirubinemia, general edema, gamma glutamyl transpeptidase increase, and hyperglycemia.

1186 **Musculoskeletal System: Infrequent:** Arthritis, leg cramps, myasthenia, and twitching.
1187 **Rare:** Bursitis, joint disorder, muscle atrophy, pathological fracture, and tendinous contracture.

1188 **Nervous System: Frequent:** Confusion and paresthesia. **Infrequent:** Akathisia, apathy,
1189 aphasia, CNS depression, depersonalization, dysarthria, dyskinesia, euphoria, hallucinations,
1190 hostility, hyperkinesia, hypertonia, libido decreased, memory decrease, mind racing, movement
1191 disorder, myoclonus, panic attack, paranoid reaction, personality disorder, psychosis, sleep
1192 disorder, stupor, and suicidal ideation. **Rare:** Cerebellar syndrome, cerebrovascular accident,
1193 cerebral sinus thrombosis, choreoathetosis, CNS stimulation, delirium, delusions, dysphoria,
1194 dystonia, extrapyramidal syndrome, faintness, grand mal convulsions, hemiplegia, hyperalgesia,
1195 hyperesthesia, hypokinesia, hypotonia, manic depression reaction, muscle spasm, neuralgia,
1196 neurosis, paralysis, and peripheral neuritis.

1197 **Respiratory System: Infrequent:** Yawn. **Rare:** Hiccup and hyperventilation.

1198 **Special Senses: Frequent:** Amblyopia. **Infrequent:** Abnormality of accommodation,
1199 conjunctivitis, dry eyes, ear pain, photophobia, taste perversion, and tinnitus. **Rare:** Deafness,
1200 lacrimation disorder, oscillopsia, parosmia, ptosis, strabismus, taste loss, uveitis, and visual field
1201 defect.

1202 **Urogenital System: Infrequent:** Abnormal ejaculation, breast pain, hematuria, impotence,
1203 menorrhagia, polyuria, urinary incontinence, and urine abnormality. **Rare:** Acute kidney failure,

1204 anorgasmia, breast abscess, breast neoplasm, creatinine increase, cystitis, dysuria, epididymitis,
1205 female lactation, kidney failure, kidney pain, nocturia, urinary retention, urinary urgency, and
1206 vaginal moniliasis.

1207 **Postmarketing and Other Experience:** In addition to the adverse experiences reported
1208 during clinical testing of LAMICTAL, the following adverse experiences have been reported in
1209 patients receiving marketed LAMICTAL and from worldwide noncontrolled investigational use.
1210 These adverse experiences have not been listed above, and data are insufficient to support an
1211 estimate of their incidence or to establish causation.

1212 **Blood and Lymphatic:** Agranulocytosis, aplastic anemia, disseminated intravascular
1213 coagulation, hemolytic anemia, neutropenia, pancytopenia, red cell aplasia.

1214 **Gastrointestinal:** Esophagitis.

1215 **Hepatobiliary Tract and Pancreas:** Pancreatitis.

1216 **Immunologic:** Lupus-like reaction, vasculitis.

1217 **Lower Respiratory:** Apnea.

1218 **Musculoskeletal:** Rhabdomyolysis has been observed in patients experiencing
1219 hypersensitivity reactions.

1220 **Neurology:** Exacerbation of parkinsonian symptoms in patients with pre-existing
1221 Parkinson's disease, tics.

1222 **Non-site Specific:** Hypersensitivity reaction, multiorgan failure, progressive
1223 immunosuppression.

1224 **DRUG ABUSE AND DEPENDENCE**

1225 The abuse and dependence potential of LAMICTAL have not been evaluated in human
1226 studies.

1227 **OVERDOSAGE**

1228 **Human Overdose Experience:** Overdoses involving quantities up to 15 g have been
1229 reported for LAMICTAL, some of which have been fatal. Overdose has resulted in ataxia,
1230 nystagmus, increased seizures, decreased level of consciousness, coma, and intraventricular
1231 conduction delay.

1232 **Management of Overdose:** There are no specific antidotes for LAMICTAL. Following a
1233 suspected overdose, hospitalization of the patient is advised. General supportive care is
1234 indicated, including frequent monitoring of vital signs and close observation of the patient. If
1235 indicated, emesis should be induced or gastric lavage should be performed; usual precautions
1236 should be taken to protect the airway. It should be kept in mind that lamotrigine is rapidly
1237 absorbed (see CLINICAL PHARMACOLOGY). It is uncertain whether hemodialysis is an
1238 effective means of removing lamotrigine from the blood. In 6 renal failure patients, about 20% of
1239 the amount of lamotrigine in the body was removed by hemodialysis during a 4-hour session. A
1240 Poison Control Center should be contacted for information on the management of overdosage of
1241 LAMICTAL.

1242 **DOSAGE AND ADMINISTRATION**

1243 **Epilepsy:**

1244 **Adjunctive Use:** LAMICTAL is indicated as adjunctive therapy for partial seizures, the
1245 generalized seizures of Lennox-Gastaut syndrome, and primary generalized tonic-clonic seizures
1246 in adult and pediatric patients (≥ 2 years of age).

1247 **Monotherapy Use:** LAMICTAL is indicated for conversion to monotherapy in adults with
1248 partial seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital,
1249 primidone, or valproate as the single AED.

1250 **Safety and effectiveness of LAMICTAL have not been established (1) as initial**
1251 **monotherapy, (2) for conversion to monotherapy from AEDs other than carbamazepine,**
1252 **phenytoin, phenobarbital, primidone, or valproate, or (3) for simultaneous conversion to**
1253 **monotherapy from 2 or more concomitant AEDs.**

1254 **Bipolar Disorder:** LAMICTAL is indicated for the maintenance treatment of Bipolar I
1255 Disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania,
1256 mixed episodes) in patients treated for acute mood episodes with standard therapy. The
1257 effectiveness of LAMICTAL in the acute treatment of mood episodes has not been established.

1258 **General Dosing Considerations for Epilepsy and Bipolar Disorder Patients:** The
1259 risk of nonserious rash is increased when the recommended initial dose and/or the rate of dose
1260 escalation of LAMICTAL is exceeded. There are suggestions, yet to be proven, that the risk of
1261 severe, potentially life-threatening rash may be increased by (1) coadministration of LAMICTAL
1262 with valproate, (2) exceeding the recommended initial dose of LAMICTAL, or (3) exceeding the
1263 recommended dose escalation for LAMICTAL. However, cases have been reported in the
1264 absence of these factors (see BOX WARNING). Therefore, it is important that the dosing
1265 recommendations be followed closely.

1266 It is recommended that LAMICTAL not be restarted in patients who discontinued due to rash
1267 associated with prior treatment with LAMICTAL, unless the potential benefits clearly outweigh
1268 the risks. If the decision is made to restart a patient who has discontinued LAMICTAL, the need
1269 to restart with the initial dosing recommendations should be assessed. The greater the interval of
1270 time since the previous dose, the greater consideration should be given to restarting with the
1271 initial dosing recommendations. If a patient has discontinued LAMICTAL for a period of more
1272 than 5 half-lives, it is recommended that initial dosing recommendations and guidelines be
1273 followed.

1274 **LAMICTAL Added to Drugs Known to Induce or Inhibit Glucuronidation:** Drugs
1275 other than those listed in PRECAUTIONS: Drug Interactions have not been systematically
1276 evaluated in combination with LAMICTAL. Since lamotrigine is metabolized predominantly by
1277 glucuronic acid conjugation, drugs that are known to induce or inhibit glucuronidation may
1278 affect the apparent clearance of lamotrigine and doses of LAMICTAL may require adjustment
1279 based on clinical response.

1280 **Target Plasma Levels for Patients With Epilepsy or Bipolar Disorder:** A
1281 therapeutic plasma concentration range has not been established for lamotrigine. Dosing of
1282 LAMICTAL should be based on therapeutic response.

1283 The half-life of LAMICTAL is affected by other concomitant medications (see CLINICAL
1284 PHARMACOLOGY: Pharmacokinetics and Drug Metabolism).

1285 See also DOSAGE AND ADMINISTRATION: Special Populations.

1286 **Special Populations: Women and Oral Contraceptives: Starting LAMICTAL in**
1287 **Women Taking Oral Contraceptives:** Although estrogen-containing oral contraceptives
1288 have been shown to increase the clearance of lamotrigine (see PRECAUTIONS: Drug
1289 Interactions), no adjustments to the recommended dose escalation guidelines for LAMICTAL
1290 should be necessary solely based on the use of estrogen-containing oral contraceptives.
1291 Therefore, dose escalation should follow the recommended guidelines for initiating adjunctive
1292 therapy with LAMICTAL based on the concomitant AED (see Table 12). See below for
1293 adjustments to maintenance doses of LAMICTAL in women taking estrogen-containing oral
1294 contraceptives.

1295 **Adjustments to the Maintenance Dose of LAMICTAL: (1) Taking Estrogen-**
1296 **Containing Oral Contraceptives:** For women not taking carbamazepine, phenytoin,
1297 phenobarbital, primidone, or rifampin, the maintenance dose of LAMICTAL will in most cases
1298 need to be increased, by as much as 2-fold over the recommended target maintenance dose, in
1299 order to maintain a consistent lamotrigine plasma level (see PRECAUTIONS: Drug
1300 Interactions). **(2) Starting Estrogen-Containing Oral Contraceptives:** In women taking a stable
1301 dose of LAMICTAL and not taking carbamazepine, phenytoin, phenobarbital, primidone, or
1302 rifampin, the maintenance dose will in most cases need to be increased by as much as 2-fold, in
1303 order to maintain a consistent lamotrigine plasma level. The dose increases should begin at the
1304 same time that the oral contraceptive is introduced and continue, based on clinical response, no
1305 more rapidly than 50 to 100 mg/day every week. Dose increases should not exceed the
1306 recommended rate unless lamotrigine plasma levels or clinical response support larger increases
1307 (see Table 12, column 2). Gradual transient increases in lamotrigine plasma levels may occur
1308 during the week of inactive hormonal preparation (“pill-free” week), and these increases will be
1309 greater if dose increases are made in the days before or during the week of inactive hormonal
1310 preparation. Increased lamotrigine plasma levels could result in additional adverse events, such
1311 as dizziness, ataxia, and diplopia (see PRECAUTIONS: Drug Interactions). If adverse events
1312 attributable to LAMICTAL consistently occur during the “pill-free” week, dose adjustments to
1313 the overall maintenance dose may be necessary. Dose adjustments limited to the “pill-free” week
1314 are not recommended. For women taking LAMICTAL in addition to carbamazepine, phenytoin,
1315 phenobarbital, primidone, or rifampin, no adjustment should be necessary to the dose of
1316 LAMICTAL. **(3) Stopping Estrogen-Containing Oral Contraceptives:** For women not taking
1317 carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, the maintenance dose of
1318 LAMICTAL will in most cases need to be decreased by as much as 50%, in order to maintain a
1319 consistent lamotrigine plasma level. The decrease in dose of LAMICTAL should not exceed

1320 25% of the total daily dose per week over a 2-week period, unless clinical response or
1321 lamotrigine plasma levels indicate otherwise (see PRECAUTIONS: Drug Interactions). For
1322 women taking LAMICTAL in addition to carbamazepine, phenytoin, phenobarbital, primidone,
1323 or rifampin, no adjustment to the dose of LAMICTAL should be necessary.

1324 **Women and Other Hormonal Contraceptive Preparations or Hormone**

1325 **Replacement Therapy:** The effect of other hormonal contraceptive preparations or hormone
1326 replacement therapy on the pharmacokinetics of lamotrigine has not been systematically
1327 evaluated. It has been reported that ethinylestradiol, not progestogens, increased the clearance of
1328 lamotrigine up to 2-fold, and the progestin only pills had no effect on lamotrigine plasma levels.
1329 Therefore, adjustments to the dosage of LAMICTAL in the presence of progestogens alone will
1330 likely not be needed.

1331 **Patients With Hepatic Impairment:** Experience in patients with hepatic impairment is
1332 limited. Based on a clinical pharmacology study in 24 patients with mild, moderate, and severe
1333 liver dysfunction (see CLINICAL PHARMACOLOGY), the following general
1334 recommendations can be made. No dosage adjustment is needed in patients with mild liver
1335 impairment. Initial, escalation, and maintenance doses should generally be reduced by
1336 approximately 25% in patients with moderate and severe liver impairment without ascites and
1337 50% in patients with severe liver impairment with ascites. Escalation and maintenance doses
1338 may be adjusted according to clinical response.

1339 **Patients With Renal Functional Impairment:** Initial doses of LAMICTAL should be
1340 based on patients' AED regimen (see above); reduced maintenance doses may be effective for
1341 patients with significant renal functional impairment (see CLINICAL PHARMACOLOGY).
1342 Few patients with severe renal impairment have been evaluated during chronic treatment with
1343 LAMICTAL. Because there is inadequate experience in this population, LAMICTAL should be
1344 used with caution in these patients.

1345 **Epilepsy:**

1346 **Adjunctive Therapy With LAMICTAL for Epilepsy:** This section provides specific
1347 dosing recommendations for patients 2 to 12 years of age and patients greater than 12 years of
1348 age. Within each of these age-groups, specific dosing recommendations are provided depending
1349 upon concomitant AED (Table 10 for patients 2 to 12 years of age and Table 12 for patients
1350 greater than 12 years of age). A weight-based dosing guide for pediatric patients on concomitant
1351 valproate is provided in Table 11.

1352 **Patients 2 to 12 Years of Age:** Recommended dosing guidelines are summarized in
1353 Table 10.

1354 Note that some of the starting doses and dose escalations listed in Table 10 are different than
1355 those used in clinical trials; however, the maintenance doses are the same as in clinical trials.
1356 Smaller starting doses and slower dose escalations than those used in clinical trials are
1357 recommended because of the suggestions that the risk of rash may be decreased by smaller
1358 starting doses and slower dose escalations. Therefore, maintenance doses will take longer to
1359 reach in clinical practice than in clinical trials. It may take several weeks to months to achieve an

1360 individualized maintenance dose. Maintenance doses in patients weighing less than 30 kg,
 1361 regardless of age or concomitant AED, may need to be increased as much as 50%, based on
 1362 clinical response.

1363 **The smallest available strength of LAMICTAL Chewable Dispersible Tablets is 2 mg,**
 1364 **and only whole tablets should be administered. If the calculated dose cannot be achieved**
 1365 **using whole tablets, the dose should be rounded down to the nearest whole tablet (see**
 1366 **HOW SUPPLIED and PATIENT INFORMATION for a description of the available sizes**
 1367 **of LAMICTAL Chewable Dispersible Tablets).**

1368
 1369 **Table 10. Escalation Regimen for LAMICTAL in Patients 2 to 12 Years of Age With**
 1370 **Epilepsy**

	For Patients Taking Valproate (see Table 11 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 11 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 11 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

1371 **Note: Only whole tablets should be used for dosing**

1372 * Rifampin and estrogen-containing oral contraceptives have also been shown to increase the
1373 apparent clearance of lamotrigine (see PRECAUTIONS: Drug Interactions).

1374

1375 **Table 11. The Initial Weight-Based Dosing Guide for Patients 2 to 12 Years Taking**
1376 **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

1377

1378 **Patients Over 12 Years of Age:** Recommended dosing guidelines are summarized in
1379 Table 12.

1380

1381 **Table 12. Escalation Regimen for LAMICTAL in Patients Over 12 Years of Age With**
 1382 **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).

1383 * Rifampin and estrogen-containing oral contraceptives have also been shown to increase the
 1384 apparent clearance of lamotrigine (see PRECAUTIONS: Drug Interactions).
 1385

1386 **Conversion From Adjunctive Therapy With Carbamazepine, Phenytoin,**
 1387 **Phenobarbital, Primidone, or Valproate as the Single AED to Monotherapy With**
 1388 **LAMICTAL in Patients ≥16 Years of Age With Epilepsy:** The goal of the transition
 1389 regimen is to effect the conversion to monotherapy with LAMICTAL under conditions that
 1390 ensure adequate seizure control while mitigating the risk of serious rash associated with the rapid
 1391 titration of LAMICTAL.

1392 The recommended maintenance dose of LAMICTAL as monotherapy is 500 mg/day given in
 1393 2 divided doses.

1394 To avoid an increased risk of rash, the recommended initial dose and subsequent dose
 1395 escalations of LAMICTAL should not be exceeded (see BOX WARNING).

1396 **Conversion From Adjunctive Therapy With Carbamazepine, Phenytoin,**
 1397 **Phenobarbital, or Primidone to Monotherapy With LAMICTAL:** After achieving a dose
 1398 of 500 mg/day of LAMICTAL according to the guidelines in Table 12, the concomitant AED
 1399 should be withdrawn by 20% decrements each week over a 4-week period. The regimen for the
 1400 withdrawal of the concomitant AED is based on experience gained in the controlled
 1401 monotherapy clinical trial.

1402 **Conversion From Adjunctive Therapy With Valproate to Monotherapy With**
 1403 **LAMICTAL:** The conversion regimen involves 4 steps (see Table 13).

1404
1405
1406

Table 13. Conversion From Adjunctive Therapy With Valproate to Monotherapy With 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 12 (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.

1407

1408 **Conversion From Adjunctive Therapy With Antiepileptic Drugs Other Than**
1409 **Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate to**

1410 **Monotherapy With LAMICTAL:** No specific dosing guidelines can be provided for
1411 conversion to monotherapy with LAMICTAL with AEDs other than carbamazepine,
1412 phenobarbital, phenytoin, primidone, or valproate.

1413 **Usual Maintenance Dose for Epilepsy:** The usual maintenance doses identified in
1414 Tables 10-12 are derived from dosing regimens employed in the placebo-controlled adjunctive
1415 studies in which the efficacy of LAMICTAL was established. In patients receiving multidrug
1416 regimens employing carbamazepine, phenytoin, phenobarbital, or primidone **without valproate**,
1417 maintenance doses of adjunctive LAMICTAL as high as 700 mg/day have been used. In patients
1418 receiving **valproate alone**, maintenance doses of adjunctive LAMICTAL as high as 200 mg/day
1419 have been used. The advantage of using doses above those recommended in Tables 10-13 has not
1420 been established in controlled trials.

1421 **Discontinuation Strategy for Patients With Epilepsy:** For patients receiving
1422 LAMICTAL in combination with other AEDs, a reevaluation of all AEDs in the regimen should
1423 be considered if a change in seizure control or an appearance or worsening of adverse
1424 experiences is observed.

1425 If a decision is made to discontinue therapy with LAMICTAL, a step-wise reduction of dose
1426 over at least 2 weeks (approximately 50% per week) is recommended unless safety concerns
1427 require a more rapid withdrawal (see PRECAUTIONS).

1428 *Discontinuing carbamazepine, phenytoin, phenobarbital, or primidone should prolong the*
1429 *half-life of lamotrigine; discontinuing valproate should shorten the half-life of lamotrigine.*

1430 **Bipolar Disorder:** The goal of maintenance treatment with LAMICTAL is to delay the time to
 1431 occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated
 1432 for acute mood episodes with standard therapy. The target dose of LAMICTAL is 200 mg/day
 1433 (100 mg/day in patients taking valproate, which decreases the apparent clearance of lamotrigine,
 1434 and 400 mg/day in patients not taking valproate and taking either carbamazepine, phenytoin,
 1435 phenobarbital, primidone, or rifampin, which increase the apparent clearance of lamotrigine). In
 1436 the clinical trials, doses up to 400 mg/day as monotherapy were evaluated, however, no
 1437 additional benefit was seen at 400 mg/day compared to 200 mg/day (see CLINICAL STUDIES:
 1438 Bipolar Disorder). Accordingly, doses above 200 mg/day are not recommended. Treatment with
 1439 LAMICTAL is introduced, based on concurrent medications, according to the regimen outlined
 1440 in Table 14. If other psychotropic medications are withdrawn following stabilization, the dose of
 1441 LAMICTAL should be adjusted. For patients discontinuing valproate, the dose of LAMICTAL
 1442 should be doubled over a 2-week period in equal weekly increments (see Table 15). For patients
 1443 discontinuing carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, the dose of
 1444 LAMICTAL should remain constant for the first week and then should be decreased by half over
 1445 a 2-week period in equal weekly decrements (see Table 15). The dose of LAMICTAL may then
 1446 be further adjusted to the target dose (200 mg) as clinically indicated.

1447 Dosage adjustments will be necessary in most patients who start or stop estrogen-containing
 1448 oral contraceptives while taking LAMICTAL (see DOSAGE AND ADMINISTRATION:
 1449 Special Populations: Women and Oral Contraceptives: Adjustments to the Maintenance Dose of
 1450 LAMICTAL).

1451 If other drugs are subsequently introduced, the dose of LAMICTAL may need to be adjusted.
 1452 In particular, the introduction of valproate requires reduction in the dose of LAMICTAL (see
 1453 CLINICAL PHARMACOLOGY: Drug Interactions).

1454 To avoid an increased risk of rash, the recommended initial dose and subsequent dose
 1455 escalations of LAMICTAL should not be exceeded (see BOX WARNING).

1456

1457 **Table 14. Escalation Regimen for LAMICTAL for Patients With Bipolar Disorder***

	For Patients Taking Valproate [‡]	For Patients Not Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Rifampin [†] and Not Taking Valproate [‡]	For Patients Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Rifampin [†] and Not Taking Valproate [‡]
Weeks 1 and 2	25 mg every <i>other</i> day	25 mg daily	50 mg daily
Weeks 3 and 4	25 mg daily	50 mg daily	100 mg daily, in divided doses
Week 5	50 mg daily	100 mg daily	200 mg daily, in divided

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

1458 * See CLINICAL PHARMACOLOGY: Drug Interactions and PRECAUTIONS: Drug
1459 Interactions for a description of known drug interactions.

1460 † Carbamazepine, phenytoin, phenobarbital, primidone, and rifampin have been shown to
1461 increase the apparent clearance of lamotrigine.

1462 ‡ Valproate has been shown to decrease the apparent clearance of lamotrigine.

1463

1464 **Table 15. Adjustments to LAMICTAL Dosing for Patients With Bipolar Disorder**
1465 **Following Discontinuation of Psychotropic Medications***

	Discontinuation of Psychotropic Drugs (excluding Carbamazepine, Phenytoin, Phenobarbital, Primidone, Rifampin†, or Valproate‡)	After Discontinuation of Valproate‡	After Discontinuation of Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Rifampin†
		Current LAMICTAL dose (mg/day)	Current LAMICTAL dose (mg/day)
		100	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

1466 * See CLINICAL PHARMACOLOGY: Drug Interactions and PRECAUTIONS: Drug
1467 Interactions for a description of known drug interactions.

1468 † Carbamazepine, phenytoin, phenobarbital, primidone, and rifampin have been shown to
1469 increase the apparent clearance of lamotrigine.

1470 ‡ Valproate has been shown to decrease the apparent clearance of lamotrigine.

1471

1472 There is no body of evidence available to answer the question of how long the patient should
1473 remain on LAMICTAL therapy. Systematic evaluation of the efficacy of LAMICTAL in patients
1474 with either depression or mania who responded to standard therapy during an acute 8 to 16 week
1475 treatment phase and were then randomized to LAMICTAL or placebo for up to 76 weeks of
1476 observation for affective relapse demonstrated a benefit of such maintenance treatment (see
1477 CLINICAL STUDIES: Bipolar Disorder). Nevertheless, patients should be periodically
1478 reassessed to determine the need for maintenance treatment.

1479 **Discontinuation Strategy in Bipolar Disorder:** As with other AEDs, LAMICTAL
1480 should not be abruptly discontinued. In the controlled clinical trials, there was no increase in the
1481 incidence, type, or severity of adverse experiences following abrupt termination of LAMICTAL.
1482 In clinical trials in patients with bipolar disorder, 2 patients experienced seizures shortly after
1483 abrupt withdrawal of LAMICTAL. However, there were confounding factors that may have
1484 contributed to the occurrence of seizures in these bipolar patients. Discontinuation of
1485 LAMICTAL should involve a step-wise reduction of dose over at least 2 weeks (approximately
1486 50% per week) unless safety concerns require a more rapid withdrawal.

1487 **Administration of LAMICTAL Chewable Dispersible Tablets:** LAMICTAL Chewable
1488 Dispersible Tablets may be swallowed whole, chewed, or dispersed in water or diluted fruit
1489 juice. If the tablets are chewed, consume a small amount of water or diluted fruit juice to aid in
1490 swallowing.

1491 To disperse LAMICTAL Chewable Dispersible Tablets, add the tablets to a small amount of
1492 liquid (1 teaspoon, or enough to cover the medication). Approximately 1 minute later, when the
1493 tablets are completely dispersed, swirl the solution and consume the entire quantity immediately.
1494 *No attempt should be made to administer partial quantities of the dispersed tablets.*

1495 **HOW SUPPLIED**

1496 **LAMICTAL Tablets, 25-mg**

1497 White, scored, shield-shaped tablets debossed with "LAMICTAL" and "25", bottles of 100
1498 (NDC 0173-0633-02).

1499 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled
1500 Room Temperature] in a dry place.**

1501 **LAMICTAL Tablets, 100-mg**

1502 Peach, scored, shield-shaped tablets debossed with "LAMICTAL" and "100", bottles of 100
1503 (NDC 0173-0642-55).

1504 **LAMICTAL Tablets, 150-mg**

1505 Cream, scored, shield-shaped tablets debossed with "LAMICTAL" and "150", bottles of 60
1506 (NDC 0173-0643-60).

1507 **LAMICTAL Tablets, 200-mg**

1508 Blue, scored, shield-shaped tablets debossed with "LAMICTAL" and "200", bottles of 60
1509 (NDC 0173-0644-60).

1510 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled
1511 Room Temperature] in a dry place and protect from light.**

1512

1513 **LAMICTAL Chewable Dispersible Tablets, 2-mg**

1514 White to off-white, round tablets debossed with "LTG" over "2", bottles of 30 (NDC 0173-
1515 0699-00). ORDER DIRECTLY FROM GlaxoSmithKline 1-800-334-4153.

1516 **LAMICTAL Chewable Dispersible Tablets, 5-mg**

1517 White to off-white, caplet-shaped tablets debossed with “GX CL2”, bottles of 100 (NDC
1518 0173-0526-00).

1519 **LAMICTAL Chewable Dispersible Tablets, 25-mg**

1520 White, super elliptical-shaped tablets debossed with “GX CL5”, bottles of 100 (NDC 0173-
1521 0527-00).

1522 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled**
1523 **Room Temperature] in a dry place.**

1524

1525 **LAMICTAL Starter Kit for Patients Taking Valproate**

1526 **25-mg**, white, scored, shield-shaped tablets debossed with "LAMICTAL" and "25",
1527 blisterpack of 35 tablets (NDC 0173-0633-10).

1528 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled**
1529 **Room Temperature] in a dry place.**

1530

1531 **LAMICTAL Starter Kit for Patients Taking Carbamazepine, Phenytoin, Phenobarbital,**
1532 **Primidone, or Rifampin and Not Taking Valproate**

1533 **25-mg**, white, scored, shield-shaped tablets debossed with "LAMICTAL" and "25" and
1534 **100-mg**, peach, scored, shield-shaped tablets debossed with "LAMICTAL" and “100”,
1535 blisterpack of 84, 25-mg tablets and 14, 100-mg tablets (NDC 0173-0594-01)

1536 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled**
1537 **Room Temperature] in a dry place and protect from light.**

1538

1539 **LAMICTAL Starter Kit for Patients Not Taking Carbamazepine, Phenytoin,**
1540 **Phenobarbital, Primidone, Rifampin, or Valproate**

1541 **25-mg**, white, scored, shield-shaped tablets debossed with "LAMICTAL" and "25" and
1542 **100-mg**, peach, scored, shield-shaped tablets debossed with "LAMICTAL" and “100”,
1543 blisterpack of 42, 25-mg tablets and 7, 100-mg tablets (NDC 0173-0594-02).

1544 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled**
1545 **Room Temperature] in a dry place and protect from light.**

1546 **PATIENT INFORMATION**

1547 The following wording is contained in a separate leaflet accompanying the product.

1548

1549

1550

1 **MEDICATION GUIDE**

2
3 **LAMICTAL (la-MIK-tal)**
4 **(lamotrigine)**

5 **Tablets**

6 **Chewable Dispersible Tablets**

7
8
9 Read this Medication Guide before you start taking LAMICTAL and each time you get a refill.
10 There may be new information. This information does not take the place of talking with your
11 healthcare provider about your medical condition or treatment. If you have questions about
12 LAMICTAL, ask your healthcare provider or pharmacist.

13
14 **What is the most important information I should know about LAMICTAL?**

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

17 There is no way to tell if a mild rash will develop into a more serious reaction. These serious
18 skin reactions are more likely to happen when you begin taking LAMICTAL, within the first 2
19 to 8 weeks of treatment. But it can happen in people who have taken LAMICTAL for any
20 period of time. Children between 2 to 16 years of age have a higher chance of getting this
21 serious skin reaction while taking LAMICTAL.

22
23 The risk of getting a rash is higher if you:

- 24 • take LAMICTAL while taking valproate (DEPAKENE (valproic acid) or DEPAKOTE
25 (divalproex sodium)).
26 • take a higher starting dose of LAMICTAL than your healthcare provider prescribed.
27 • increase your dose of LAMICTAL faster than prescribed.
28

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

32
33 **Call your healthcare provider right away if you have any of the following:**

- 34 • **a skin rash**
35 • **hives**
36 • **fever**
37 • **swollen lymph glands**
38 • **painful sores in the mouth or around your eyes**
39 • **swelling of your lips or tongue**
40 • **yellowing of your skin or eyes**
41 • **unusual bruising or bleeding**
42 • **severe fatigue or weakness**
43 • **severe muscle pain**

- 44 • **frequent infections**
45

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

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

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

- 52 • thoughts about suicide or dying
53 • attempt to commit suicide
54 • new or worse depression
55 • new or worse anxiety
56 • feeling agitated or restless
57 • panic attacks
58 • trouble sleeping (insomnia)
59 • new or worse irritability
60 • acting aggressive, being angry, or violent
61 • acting on dangerous impulses
62 • an extreme increase in activity and talking (mania)
63 • other unusual changes in behavior or mood

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

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

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

- 69 • Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts,
70 or feelings.
71 • Keep all follow-up visits with your healthcare provider as scheduled.
72 • Call your healthcare provider between visits as needed, especially if you are worried
73 about symptoms.

74 **LAMICTAL can have other serious side effects.** For more information ask your healthcare
75 provider or pharmacist. Tell your healthcare provider if you have any side effect that bothers
76 you. Be sure to read the section below entitled "What are the possible side effects of
77 LAMICTAL?"

- 78 **3. Patients prescribed LAMICTAL have sometimes been given the wrong medicine**
79 **because many medicines have names similar to LAMICTAL, so always check that you**
80 **receive LAMICTAL.**





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

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




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88 These pictures show the distinct wording, colors, and shapes of the tablets that help to
 89 identify the right strength of LAMICTAL Tablets and Chewable Dispersible Tablets.
 90 Immediately call your pharmacist if you receive a LAMICTAL tablet that does not look like
 91 one of the tablets shown below, as you may have received the wrong medication.

92
 93 **LAMICTAL (lamotrigine) Tablets**
 94

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

95
 96 **LAMICTAL (lamotrigine) Chewable Dispersible Tablets**
 97

 2 mg, white Imprinted with LTG 2	 5 mg, white Imprinted with GX CL2	 25 mg, white Imprinted with GX CL5
--	--	--

98
 99
 100 **What is LAMICTAL?**
 101

102 LAMICTAL is a prescription medicine used:

- 103 1. together with other medicines to treat certain types of seizures (partial seizures, primary
 104 generalized tonic-clonic seizures, generalized seizures of Lennox-Gastaut syndrome) in
 105 people 2 years or older.
- 106 2. alone when changing from other medicines used to treat partial seizures in people 16 years
 107 or older.
- 108 3. for the long-term treatment of Bipolar I Disorder to lengthen the time between mood
 109 episodes in people 18 years or older who have been treated for mood episodes with other
 110 medicine.

111 It is not known if LAMICTAL is safe or effective in children or teenagers under the age of 18 with
 112 mood disorders such as bipolar disorder or depression.

113 It is not known if LAMICTAL is safe or effective when used alone as the first treatment of
 114 seizures in adults.

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Who should not take LAMICTAL?

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

What should I tell my healthcare provider before taking LAMICTAL?

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

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

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

How should I take LAMICTAL?

- Take LAMICTAL exactly as prescribed.
- Your healthcare provider may change your dose. Do not change your dose without talking to your healthcare provider.
- Do not stop taking LAMICTAL without talking to your healthcare provider. Stopping LAMICTAL suddenly may cause serious problems. For example, if you have epilepsy and you stop taking LAMICTAL suddenly, you may get seizures that do not stop. Talk with your healthcare provider about how to stop LAMICTAL slowly.
- If you miss a dose of LAMICTAL, take it as soon as you remember. If it is almost time for your next dose, just skip the missed dose. Take the next dose at your regular time. **Do**

157 **not take two doses at the same time.**

- 158 • You may not feel the full effect of LAMICTAL for several weeks.
- 159 • If you have epilepsy, tell your healthcare provider if your seizures get worse or if you have
160 any new types of seizures.
- 161 • Swallow LAMICTAL tablets whole.
- 162 • LAMICTAL Chewable Dispersible tablets may be swallowed whole, chewed, or mixed in
163 water or diluted fruit juice. If the tablets are chewed, drink a small amount of water or diluted
164 fruit juice to help in swallowing. To break up LAMICTAL Chewable Dispersible tablets, add
165 the tablets to a small amount of liquid (1 teaspoon, or enough to cover the medicine) in a
166 glass or spoon. Wait at least 1 minute or until the tablets are completely broken up, mix the
167 solution together and take the whole amount right away.

168

169 **What should I avoid while taking LAMICTAL?**

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

172

173 **What are possible side effects of LAMICTAL?**

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

175 Common side effects of LAMICTAL include:

176

- dizziness
- headache
- blurred or double vision
- lack of coordination
- sleepiness
- nausea, vomiting
- insomnia
- tremor
- rash
- fever
- abdominal pain
- back pain
- tiredness
- dry mouth

177

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

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

181 Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-
182 800-FDA-1088.

183

184 **How should I store LAMICTAL?**

- 185 • Store LAMICTAL at room temperature between 68°F to 77°F (20°C to 25°C).
- 186 • **Keep LAMICTAL and all medicines out of the reach of children.**

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General information about LAMICTAL

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

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

For more information, go to www.lamictal.com or call 1-888-825-5249.

What are the ingredients in LAMICTAL?

LAMICTAL Tablets

Active ingredient: lamotrigine.

Inactive ingredients: lactose; magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate, FD&C Yellow No. 6 Lake (100-mg tablet only), ferric oxide, yellow (150-mg tablet only), and FD&C Blue No. 2 Lake (200-mg tablet only).

LAMICTAL Chewable Dispersible Tablets

Active ingredient: lamotrigine.

Inactive ingredients: blackcurrant flavor, calcium carbonate, low-substituted hydroxypropylcellulose, magnesium aluminum silicate, magnesium stearate, povidone, saccharin sodium, and sodium starch glycolate.

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

(Date of Issue)

LMT: XMG



Manufactured for
GlaxoSmithKline
Research Triangle Park, NC 27709
by DSM Pharmaceuticals, Inc.
Greenville, NC 27834 or
GlaxoSmithKline

224 Research Triangle Park, NC 27709

225

226 LAMICTAL is a registered trademark of GlaxoSmithKline.*DEPAKENE and DEPAKOTE are
227 registered trademarks of Abbott Laboratories.

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231 April 2009

232 LMT:1MG

NDA 20-241 Lamictal (lamotrigine) Tablets

NDA 20-764 Lamictal (lamotrigine) Chewable Dispersible Tablets

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL:

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

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each LAMICTAL prescription.

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

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

B. Communication Plan

Not applicable.

C. Elements to Assure Safe Use

Not applicable.

D. Implementation System

Not applicable.

III. Timetable for Submission of Assessments

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

APPENDIX 1: Specifications and Justification for Supply of Medication Guide

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

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

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

Dispense the enclosed Medication Guide to each patient.

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

Dispense the accompanying Medication Guide to each patient.

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

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

	100 mg x 100 tablets (Trade)	3	N: 88 P: 50	N: 90 P: 50	N: 91 P: 50
	150 mg x 60 tablets (Trade)	2			
	200 mg x 60 tablets (Trade)	2			

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

† Inpatient Use Only (exempt)

APPENDIX 2: REMS Assessments

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

The following assessments are planned:

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

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

