

**LAMICTAL<sup>®</sup>**  
**(lamotrigine)**  
**Tablets**

**LAMICTAL<sup>®</sup>**  
**(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.

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

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

39 **ESCALATION FOR LAMICTAL. HOWEVER, CASES HAVE BEEN REPORTED IN**  
40 **THE ABSENCE OF THESE FACTORS.**

41 **NEARLY ALL CASES OF LIFE-THREATENING RASHES ASSOCIATED WITH**  
42 **LAMICTAL HAVE OCCURRED WITHIN 2 TO 8 WEEKS OF TREATMENT**  
43 **INITIATION. HOWEVER, ISOLATED CASES HAVE BEEN REPORTED AFTER**  
44 **PROLONGED TREATMENT (E.G., 6 MONTHS). ACCORDINGLY, DURATION OF**  
45 **THERAPY CANNOT BE RELIED UPON AS A MEANS TO PREDICT THE**  
46 **POTENTIAL RISK HERALDED BY THE FIRST APPEARANCE OF A RASH.**

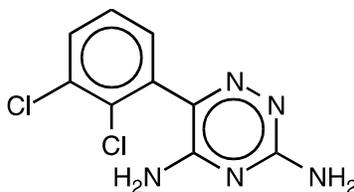
47 **ALTHOUGH BENIGN RASHES ALSO OCCUR WITH LAMICTAL, IT IS NOT**  
48 **POSSIBLE TO PREDICT RELIABLY WHICH RASHES WILL PROVE TO BE**  
49 **SERIOUS OR LIFE THREATENING. ACCORDINGLY, LAMICTAL SHOULD**  
50 **ORDINARILY BE DISCONTINUED AT THE FIRST SIGN OF RASH, UNLESS THE**  
51 **RASH IS CLEARLY NOT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

54

## 55 **DESCRIPTION**

56 LAMICTAL (lamotrigine), an antiepileptic drug (AED) of the phenyltriazine class, is  
57 chemically unrelated to existing antiepileptic drugs. Its chemical name is 3,5-diamino-6-(2,3-  
58 dichlorophenyl)-*as*-triazine, its molecular formula is  $C_9H_7N_5Cl_2$ , and its molecular weight is  
59 256.09. Lamotrigine is a white to pale cream-colored powder and has a  $pK_a$  of 5.7. Lamotrigine  
60 is very slightly soluble in water (0.17 mg/mL at 25°C) and slightly soluble in 0.1 M HCl  
61 (4.1 mg/mL at 25°C). The structural formula is:

62



63

64

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

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

75 **CLINICAL PHARMACOLOGY**

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

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

87 LAMICTAL also displayed inhibitory properties in the kindling model in rats both during  
88 kindling development and in the fully kindled state. The relevance of this animal model to  
89 specific types of human epilepsy is unclear.

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

92 **Pharmacological Properties:** Although the relevance for human use is unknown, the  
93 following data characterize the performance of LAMICTAL in receptor binding assays.  
94 Lamotrigine had a weak inhibitory effect on the serotonin 5-HT<sub>3</sub> receptor (IC<sub>50</sub> = 18 μM). It does  
95 not exhibit high affinity binding (IC<sub>50</sub>>100 μM) to the following neurotransmitter receptors:  
96 adenosine A<sub>1</sub> and A<sub>2</sub>; adrenergic α<sub>1</sub>, α<sub>2</sub>, and β; dopamine D<sub>1</sub> and D<sub>2</sub>; γ-aminobutyric acid  
97 (GABA) A and B; histamine H<sub>1</sub>; kappa opioid; muscarinic acetylcholine; and serotonin 5-HT<sub>2</sub>.  
98 Studies have failed to detect an effect of lamotrigine on dihydropyridine-sensitive calcium  
99 channels. It had weak effects at sigma opioid receptors (IC<sub>50</sub> = 145 μM). Lamotrigine did not  
100 inhibit the uptake of norepinephrine, dopamine, or serotonin, (IC<sub>50</sub>>200 μM) when tested in rat  
101 synaptosomes and/or human platelets in vitro.

102 **Effect of Lamotrigine on N-Methyl d-Aspartate-Receptor Mediated Activity:**  
103 Lamotrigine did not inhibit N-methyl d-aspartate (NMDA)-induced depolarizations in rat cortical  
104 slices or NMDA-induced cyclic GMP formation in immature rat cerebellum, nor did lamotrigine  
105 displace compounds that are either competitive or noncompetitive ligands at this glutamate  
106 receptor complex (CNQX, CGS, TCHP). The IC<sub>50</sub> for lamotrigine effects on NMDA-induced  
107 currents (in the presence of 3 μM of glycine) in cultured hippocampal neurons exceeded  
108 100 μM.

109 **Folate Metabolism:** In vitro, lamotrigine was shown to be an inhibitor of dihydrofolate  
110 reductase, the enzyme that catalyzes the reduction of dihydrofolate to tetrahydrofolate. Inhibition  
111 of this enzyme may interfere with the biosynthesis of nucleic acids and proteins. When oral daily  
112 doses of lamotrigine were given to pregnant rats during organogenesis, fetal, placental, and  
113 maternal folate concentrations were reduced. Significantly reduced concentrations of folate are  
114 associated with teratogenesis (see PRECAUTIONS: Pregnancy). Folate concentrations were also

115 reduced in male rats given repeated oral doses of lamotrigine. Reduced concentrations were  
116 partially returned to normal when supplemented with folic acid.

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

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

123 **Cardiovascular:** In dogs, lamotrigine is extensively metabolized to a 2-N-methyl  
124 metabolite. This metabolite causes dose-dependent prolongations of the PR interval, widening of  
125 the QRS complex, and, at higher doses, complete AV conduction block. Similar cardiovascular  
126 effects are not anticipated in humans because only trace amounts of the 2-N-methyl metabolite  
127 (<0.6% of lamotrigine dose) have been found in human urine (see Drug Disposition). However,  
128 it is conceivable that plasma concentrations of this metabolite could be increased in patients with  
129 a reduced capacity to glucuronidate lamotrigine (e.g., in patients with liver disease).

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

134

135 **Table 1. Mean\* Pharmacokinetic Parameters in Healthy Volunteers and Adult Patients**  
 136 **With Epilepsy**

Adult Study Population	Number of Subjects	T <sub>max</sub> : Time of Maximum Plasma Concentration (h)	t <sub>1/2</sub> : 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 <sup>†</sup> 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 <sup>†</sup> :				
Single-dose LAMICTAL	24	2.3 (0.5-5.0)	14.4 (6.4-30.4)	1.10 (0.51-2.22)
Multiple-dose LAMICTAL	17	2.0 (0.75-5.93)	12.6 (7.5-23.1)	1.21 (0.66-1.82)

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

142 † Carbamazepine, phenobarbital, phenytoin, and primidone have been shown to increase the  
143 apparent clearance of lamotrigine. Oral contraceptives and rifampin have also been shown to  
144 increase the apparent clearance of lamotrigine (see CLINICAL PHARMACOLOGY: Drug  
145 Interactions and PRECAUTIONS: Drug Interactions).

146

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

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

157 **Protein Binding:** Data from in vitro studies indicate that lamotrigine is approximately 55%  
158 bound to human plasma proteins at plasma lamotrigine concentrations from 1 to 10 mcg/mL  
159 (10 mcg/mL is 4 to 6 times the trough plasma concentration observed in the controlled efficacy  
160 trials). Because lamotrigine is not highly bound to plasma proteins, clinically significant  
161 interactions with other drugs through competition for protein binding sites are unlikely. The  
162 binding of lamotrigine to plasma proteins did not change in the presence of therapeutic  
163 concentrations of phenytoin, phenobarbital, or valproate. Lamotrigine did not displace other  
164 AEDs (carbamazepine, phenytoin, phenobarbital) from protein binding sites.

165 **Drug Disposition:** Lamotrigine is metabolized predominantly by glucuronic acid  
166 conjugation; the major metabolite is an inactive 2-N-glucuronide conjugate. After oral  
167 administration of 240 mg of <sup>14</sup>C-lamotrigine (15 μCi) to 6 healthy volunteers, 94% was  
168 recovered in the urine and 2% was recovered in the feces. The radioactivity in the urine consisted  
169 of unchanged lamotrigine (10%), the 2-N-glucuronide (76%), a 5-N-glucuronide (10%), a  
170 2-N-methyl metabolite (0.14%), and other unidentified minor metabolites (4%).

171 **Drug Interactions: The apparent clearance of lamotrigine is affected by the**  
172 **coadministration of certain medications.** Since lamotrigine is metabolized predominantly by  
173 glucuronic acid conjugation, drugs that induce or inhibit glucuronidation may affect the apparent  
174 clearance of lamotrigine.

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

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

179 Oral contraceptives and rifampin have also been shown to increase the apparent clearance of  
180 lamotrigine (see PRECAUTIONS: Drug Interactions).

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

188 Oxcarbazepine and levetiracetam do not affect the apparent clearance of lamotrigine (see  
189 PRECAUTIONS: Drug Interactions).

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

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

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

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

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

204 Following multiple administrations (150 mg twice daily) to normal volunteers taking no other  
205 medications, lamotrigine induced its own metabolism, resulting in a 25% decrease in  $t_{1/2}$  and a  
206 37% increase in  $Cl/F$  at steady state compared to values obtained in the same volunteers  
207 following a single dose. Evidence gathered from other sources suggests that self-induction by  
208 LAMICTAL may not occur when LAMICTAL is given as adjunctive therapy in patients  
209 receiving carbamazepine, phenytoin, phenobarbital, primidone, or rifampin.

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

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

217 **Special Populations: Patients With Renal Insufficiency:** Twelve volunteers with  
218 chronic renal failure (mean creatinine clearance = 13 mL/min; range = 6 to 23) and another  
219 6 individuals undergoing hemodialysis were each given a single 100-mg dose of LAMICTAL.  
220 The mean plasma half-lives determined in the study were 42.9 hours (chronic renal failure),  
221 13.0 hours (during hemodialysis), and 57.4 hours (between hemodialysis) compared to  
222 26.2 hours in healthy volunteers. On average, approximately 20% (range = 5.6 to 35.1) of the  
223 amount of lamotrigine present in the body was eliminated by hemodialysis during a 4-hour  
224 session.

225 **Hepatic Disease:** The pharmacokinetics of lamotrigine following a single 100-mg dose  
226 of LAMICTAL were evaluated in 24 subjects with moderate to severe hepatic dysfunction and  
227 compared with 12 subjects without hepatic impairment. The median apparent clearance of  
228 lamotrigine was 0.31, 0.24, or 0.10 mL/kg/min in patients with Grade A, B, or C (Child-Pugh  
229 Classification) hepatic impairment, respectively, compared to 0.34 mL/kg/min in the healthy  
230 controls. Median half-life of lamotrigine was 36, 60, or 110 hours in patients with Grade A, B, or  
231 C hepatic impairment, respectively, versus 32 hours in healthy controls.

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

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

249

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

Pediatric Study Population	Number of Subjects	T <sub>max</sub> (h)	t <sub>1/2</sub> (h)	Cl/F (mL/min/kg)
<b>Ages 10 months-5.3 years</b>				
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)
<b>Ages 5-11 years</b>				
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 <sup>†</sup>	3	4.5 (3.0-6.0)	65.8 (50.7-73.7)	0.24 (0.21-0.26)
<b>Ages 13-18 years</b>				
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone*	11	‡	‡	1.3
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone*	8	‡	‡	0.5
plus valproate				
Patients taking valproate only	4	‡	‡	0.3

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

255 <sup>†</sup>Two subjects were included in the calculation for mean T<sub>max</sub>.

256 <sup>‡</sup>Parameter not estimated.

257

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

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

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

## 269 **CLINICAL STUDIES**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

365 **Bipolar Disorder:** The effectiveness of LAMICTAL in the maintenance treatment of Bipolar I  
366 Disorder was established in 2 multicenter, double-blind, placebo-controlled studies in adult  
367 patients who met DSM-IV criteria for Bipolar I Disorder. Study 1 enrolled patients with a current  
368 or recent (within 60 days) depressive episode as defined by DSM-IV and Study 2 included  
369 patients with a current or recent (within 60 days) episode of mania or hypomania as defined by  
370 DSM-IV. Both studies included a cohort of patients (30% of 404 patients in Study 1 and 28% of  
371 171 patients in Study 2) with rapid cycling Bipolar Disorder (4 to 6 episodes per year).

372 In both studies, patients were titrated to a target dose of 200 mg of LAMICTAL, as add-on  
373 therapy or as monotherapy, with gradual withdrawal of any psychotropic medications during an  
374 8- to 16-week open-label period. Overall 81% of 1,305 patients participating in the open-label  
375 period were receiving 1 or more other psychotropic medications, including benzodiazepines,  
376 selective serotonin reuptake inhibitors (SSRIs), atypical antipsychotics (including olanzapine),

377 valproate, or lithium, during titration of LAMICTAL. Patients with a CGI-severity score of 3 or  
378 less maintained for at least 4 continuous weeks, including at least the final week on monotherapy  
379 with LAMICTAL, were randomized to a placebo-controlled, double-blind treatment period for  
380 up to 18 months. The primary endpoint was TIME (time to intervention for a mood episode or  
381 one that was emerging, time to discontinuation for either an adverse event that was judged to be  
382 related to Bipolar Disorder, or for lack of efficacy). The mood episode could be depression,  
383 mania, hypomania, or a mixed episode.

384 In Study 1, patients received double-blind monotherapy with LAMICTAL, 50 mg/day  
385 (n = 50), LAMICTAL 200 mg/day (n = 124), LAMICTAL 400 mg/day (n = 47), or placebo  
386 (n = 121). LAMICTAL (200- and 400-mg/day treatment groups combined) was superior to  
387 placebo in delaying the time to occurrence of a mood episode. Separate analyses of the 200 and  
388 400 mg/day dose groups revealed no added benefit from the higher dose.

389 In Study 2, patients received double-blind monotherapy with LAMICTAL (100 to  
390 400 mg/day, n = 59), or placebo (n = 70). LAMICTAL was superior to placebo in delaying time  
391 to occurrence of a mood episode. The mean LAMICTAL dose was about 211 mg/day.

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

## 396 **INDICATIONS AND USAGE**

### 397 **Epilepsy:**

398 **Adjunctive Use:** LAMICTAL is indicated as adjunctive therapy for partial seizures in  
399 adults and pediatric patients ( $\geq 2$  years of age).

400 LAMICTAL is also indicated as adjunctive therapy for the generalized seizures of  
401 Lennox-Gastaut syndrome in adult and pediatric patients ( $\geq 2$  years of age).

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

405 Safety and effectiveness of LAMICTAL have not been established (1) as initial monotherapy,  
406 (2) for conversion to monotherapy from AEDs other than carbamazepine, phenytoin,  
407 phenobarbital, primidone, or valproate, or (3) for simultaneous conversion to monotherapy from  
408 2 or more concomitant AEDs (see DOSAGE AND ADMINISTRATION).

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

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

416 The effectiveness of LAMICTAL as maintenance treatment was established in  
417 2 placebo-controlled trials of 18 months' duration in patients with Bipolar I Disorder as defined  
418 by DSM-IV (see CLINICAL STUDIES, Bipolar Disorder). The physician who elects to use  
419 LAMICTAL for periods extending beyond 18 months should periodically re-evaluate the  
420 long-term usefulness of the drug for the individual patient.

## 421 **CONTRAINDICATIONS**

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

## 424 **WARNINGS**

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

427 **ALTHOUGH BENIGN RASHES ALSO OCCUR WITH LAMICTAL, IT IS NOT**  
428 **POSSIBLE TO PREDICT RELIABLY WHICH RASHES WILL PROVE TO BE**  
429 **SERIOUS OR LIFE THREATENING. ACCORDINGLY, LAMICTAL SHOULD**  
430 **ORDINARILY BE DISCONTINUED AT THE FIRST SIGN OF RASH, UNLESS THE**  
431 **RASH IS CLEARLY NOT DRUG RELATED. DISCONTINUATION OF TREATMENT**  
432 **MAY NOT PREVENT A RASH FROM BECOMING LIFE THREATENING OR**  
433 **PERMANENTLY DISABLING OR DISFIGURING.**

434 **Serious Rash: Pediatric Population:** The incidence of serious rash associated with  
435 hospitalization and discontinuation of LAMICTAL in a prospectively followed cohort of  
436 pediatric patients with epilepsy receiving adjunctive therapy was approximately 0.8% (16 of  
437 1,983). When 14 of these cases were reviewed by 3 expert dermatologists, there was  
438 considerable disagreement as to their proper classification. To illustrate, one dermatologist  
439 considered none of the cases to be Stevens-Johnson syndrome; another assigned 7 of the 14 to  
440 this diagnosis. There was 1 rash-related death in this 1,983 patient cohort. Additionally, there  
441 have been rare cases of toxic epidermal necrolysis with and without permanent sequelae and/or  
442 death in US and foreign postmarketing experience. It bears emphasis, accordingly, that  
443 LAMICTAL is only approved for use in those patients below the age of 16 who have partial  
444 seizures or generalized seizures associated with the Lennox-Gastaut syndrome (see  
445 INDICATIONS).

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

450 **Adult Population:** Serious rash associated with hospitalization and discontinuation of  
451 LAMICTAL occurred in 0.3% (11 of 3,348) of adult patients who received LAMICTAL in  
452 premarketing clinical trials of epilepsy. In the bipolar and other mood disorders clinical trials, the  
453 rate of serious rash was 0.08% (1 of 1,233) of adult patients who received LAMICTAL as initial  
454 monotherapy and 0.13% (2 of 1,538) of adult patients who received LAMICTAL as adjunctive

455 therapy. No fatalities occurred among these individuals. However, in worldwide postmarketing  
456 experience, rare cases of rash-related death have been reported, but their numbers are too few to  
457 permit a precise estimate of the rate.

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

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

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

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

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

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

490 Additionally, 3 patients (a 45-year-old woman, a 3.5-year-old boy, and an 11-year-old girl)  
491 developed multiorgan dysfunction and disseminated intravascular coagulation 9 to 14 days after  
492 LAMICTAL was added to their AED regimens. Rash and elevated transaminases were also  
493 present in all patients and rhabdomyolysis was noted in 2 patients. Both pediatric patients were  
494 receiving concomitant therapy with valproate, while the adult patient was being treated with

495 carbamazepine and clonazepam. All patients subsequently recovered with supportive care after  
496 treatment with LAMICTAL was discontinued.

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

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

## 507 **PRECAUTIONS**

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

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

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

524 **ACCORDINGLY, LAMICTAL SHOULD ORDINARILY BE DISCONTINUED AT THE**  
525 **FIRST SIGN OF RASH, UNLESS THE RASH IS CLEARLY NOT DRUG RELATED.**  
526 **DISCONTINUATION OF TREATMENT MAY NOT PREVENT A RASH FROM**  
527 **BECOMING LIFE THREATENING OR PERMANENTLY DISABLING OR**  
528 **DISFIGURING.**

529 It is recommended that LAMICTAL not be restarted in patients who discontinued due to rash  
530 associated with prior treatment with LAMICTAL unless the potential benefits clearly outweigh  
531 the risks. If the decision is made to restart a patient who has discontinued LAMICTAL, the need  
532 to restart with the initial dosing recommendations should be assessed. The greater the interval of  
533 time since the previous dose, the greater consideration should be given to restarting with the

534 initial dosing recommendations. If a patient has discontinued LAMICTAL for a period of more  
535 than 5 half-lives, it is recommended that initial dosing recommendations and guidelines be  
536 followed. The half-life of LAMICTAL is affected by other concomitant medications (see  
537 CLINICAL PHARMACOLOGY: Pharmacokinetics and Drug Metabolism, and DOSAGE AND  
538 ADMINISTRATION).

539 **Use in Patients With Epilepsy:**

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

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

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

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

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

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

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

573 **Clinical Worsening and Suicide Risk Associated With Bipolar Disorder:** Patients  
574 with bipolar disorder may experience worsening of their depressive symptoms and/or the  
575 emergence of suicidal ideation and behaviors (suicidality) whether or not they are taking  
576 medications for bipolar disorder. Patients should be closely monitored for clinical worsening  
577 (including development of new symptoms) and suicidality, especially at the beginning of a  
578 course of treatment, or at the time of dose changes.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

636 Women should be advised to notify their physician if they plan to start or stop use of oral  
637 contraceptives or other female hormonal preparations. They should also be advised to promptly  
638 notify their physician if they experience changes in menstrual pattern (e.g., break-through  
639 bleeding) while receiving LAMICTAL in combination with these medications.

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

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

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

651 **Drug Interactions:**

652 **Effects of Lamotrigine on the Pharmacokinetics of Other Drugs:** (see Table 3).

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

662 **LAMICTAL Added to Oxcarbazepine:** The AUC and C<sub>max</sub> of oxcarbazepine and its  
663 active 10-monohydroxy oxcarbazepine metabolite were not significantly different following the  
664 addition of oxcarbazepine (600 mg twice daily) to LAMICTAL (200 mg once daily) in healthy  
665 male volunteers (n = 13) compared to healthy male volunteers receiving oxcarbazepine alone  
666 (n = 13). Limited clinical data suggest a higher incidence of headache, dizziness, nausea, and  
667 somnolence with coadministration of LAMICTAL and oxcarbazepine compared to LAMICTAL  
668 alone or oxcarbazepine alone.

669 **LAMICTAL Added to Levetiracetam:** Potential drug interactions between  
670 levetiracetam and lamotrigine were assessed by evaluating serum concentrations of both agents  
671 during placebo-controlled clinical trials. These data indicate that lamotrigine does not influence  
672 the pharmacokinetics of levetiracetam.

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

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

680 **LAMICTAL Added to Phenytoin:** LAMICTAL has no appreciable effect on  
681 steady-state phenytoin plasma concentrations in patients with epilepsy.

682 **LAMICTAL Added to Olanzapine:** The AUC and C<sub>max</sub> of olanzapine were similar  
683 following the addition of olanzapine (15 mg once daily) to LAMICTAL (200 mg once daily) in  
684 healthy male volunteers (n = 16) compared to the AUC and C<sub>max</sub> in healthy male volunteers  
685 receiving olanzapine alone (n = 16).

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

688 **Effects of Other Drugs on the Pharmacokinetics of Lamotrigine:** (see Table 3).

689 **Valproate Added to LAMICTAL:** The addition of valproate increases lamotrigine  
690 steady-state concentrations in normal volunteers by slightly more than 2-fold. In one study,

691 maximal inhibition of lamotrigine clearance was reached at valproate doses between 250 mg/day  
692 and 500 mg/day and did not increase as the valproate dose was further increased.

693 **Carbamazepine, Phenytoin, Phenobarbital, or Primidone Added to**  
694 **LAMICTAL:** The addition of these AEDs decreases lamotrigine steady-state concentrations by  
695 approximately 40%.

696 **Oxcarbazepine Added to LAMICTAL:** The AUC and  $C_{max}$  of lamotrigine were similar  
697 following the addition of oxcarbazepine (600 mg twice daily) to LAMICTAL (200 mg once  
698 daily) in healthy male volunteers (n = 13) compared to healthy male volunteers receiving  
699 LAMICTAL alone (n = 13). Limited clinical data suggest a higher incidence of headache,  
700 dizziness, nausea, and somnolence with coadministration of LAMICTAL and oxcarbazepine  
701 compared to LAMICTAL alone or oxcarbazepine alone.

702 **Levetiracetam Added to LAMICTAL:** Potential drug interactions between  
703 levetiracetam and lamotrigine were assessed by evaluating serum concentrations of both agents  
704 during placebo-controlled clinical trials. These data indicate that levetiracetam does not influence  
705 the pharmacokinetics of lamotrigine.

706 **Bupropion Added to LAMICTAL:** The pharmacokinetics of a 100-mg single dose of  
707 lamotrigine in 12 healthy volunteers were not changed by co-administration of bupropion at  
708 300 mg/day starting 11 days before the lamotrigine dose.

709 **Olanzapine Added to LAMICTAL:** The AUC and  $C_{max}$  of lamotrigine was reduced on  
710 average by 24% and 20%, respectively, following the addition of olanzapine (15 mg once daily)  
711 to LAMICTAL (200 mg once daily) in healthy male volunteers (n = 16) compared to healthy  
712 male volunteers receiving LAMICTAL alone (n = 12). This reduction in lamotrigine plasma  
713 concentrations is not expected to be clinically relevant.

714 **Other Psychotropic Drugs Added to LAMICTAL:** Results of in vitro experiments  
715 suggest that clearance of lamotrigine is unlikely to be reduced by concomitant administration of  
716 amitriptyline, clonazepam, clozapine, fluoxetine, haloperidol, lorazepam, phenelzine,  
717 risperidone, sertraline, or trazodone (see CLINICAL PHARMACOLOGY: Pharmacokinetics  
718 and Drug Metabolism).

719 **Rifampin Added to LAMICTAL:** In a study in 10 male volunteers, rifampin  
720 (600 mg/day for 5 days) significantly increased the apparent clearance of a single 25 mg dose of  
721 lamotrigine by approximately 2-fold (AUC decreased by approximately 40%).

722 **Interactions With Folate Inhibitors:** Lamotrigine is an inhibitor of dihydrofolate  
723 reductase. Prescribers should be aware of this action when prescribing other medications that  
724 inhibit folate metabolism.

725 **Interactions With Oral Contraceptives: Effect of Oral Contraceptives on**  
726 **LAMICTAL:** In a study in 16 female volunteers, an oral contraceptive preparation containing  
727 30 mcg ethinylestradiol and 150 mcg levonorgestrel increased the apparent clearance of  
728 lamotrigine (300 mg/day) by approximately two fold with a mean decrease in AUC of 52% and  
729 in  $C_{max}$  of 39%. In this study, trough serum lamotrigine concentrations gradually increased and

730 were approximately 2-fold higher on average at the end of the week of the inactive preparation  
731 compared to trough lamotrigine concentrations at the end of the active hormone cycle.

732 Gradual transient increases in lamotrigine levels will occur during the week of no active  
733 hormone preparation (pill-free week) for women not also taking a drug that increases the  
734 clearance of lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). The  
735 increase in lamotrigine levels will be greater if the dose of LAMICTAL is increased in the few  
736 days before or during the pill-free week.

737 Dosage adjustments may be necessary for women receiving oral contraceptive preparations  
738 (see DOSAGE AND ADMINISTRATION: Women and Oral Contraceptives).

739 **Effect of LAMICTAL on Oral Contraceptives:** Co-administration of LAMICTAL  
740 (300 mg/day) in 16 female volunteers did not affect the pharmacokinetics of the ethinylestradiol  
741 component of an oral contraceptive preparation containing 30 mcg ethinylestradiol and 150 mcg  
742 levonorgestrel. There was a mean decrease in the AUC and C<sub>max</sub> of the levonorgestrel component  
743 of 19% and 12%, respectively. Measurement of serum progesterone indicated that there was no  
744 hormonal evidence of ovulation in any of the 16 volunteers, although measurement of serum  
745 FSH, LH, and estradiol indicated that there was some loss of suppression of the hypothalamic-  
746 pituitary-ovarian axis.

747 The effects of doses of LAMICTAL other than 300 mg/day have not been studied.

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

752 **Interactions With Other Hormonal Contraceptives or Hormone Replacement**

753 **Therapy:** The effect of other hormonal contraceptive preparations or hormone replacement  
754 therapy on the pharmacokinetics of lamotrigine has not been evaluated, although the effect may  
755 be similar to oral contraceptive preparations. Therefore, as for oral contraceptives, dosage  
756 adjustments may be necessary (see DOSAGE AND ADMINISTRATION: Women and Oral  
757 Contraceptives).

758 The net effects of drug interactions with LAMICTAL are summarized in Table 3.

759

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

Drug	Drug Plasma Concentration With Adjunctive LAMICTAL*	Lamotrigine Plasma Concentration With Adjunctive Drugs <sup>†</sup>
Phenytoin (PHT)	↔	↓
Carbamazepine (CBZ)	↔	↓
CBZ epoxide <sup>‡</sup>	?	
Valproate	↓	↑
Valproate + PHT and/or CBZ	Not assessed	↔

Oxcarbazepine	↔	↔
10-monohydroxy oxcarbazepine metabolite§	↔	
Levetiracetam	↔	↔
Lithium	↔	Not assessed
Bupropion	Not assessed	↔
Olanzapine	↔	↔ <sup>  </sup>
Rifampin	Not assessed	↓
Ethinylestradiol/levonorgestrel <sup>¶</sup>	↔ <sup>#</sup>	↓

761 \*From adjunctive clinical trials and volunteer studies.

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

764 ‡Not administered, but an active metabolite of carbamazepine.

765 §Not administered, but an active metabolite of oxcarbazepine.

766 ↔ = No significant effect.

767 ? = Conflicting data.

768 <sup>||</sup>Slight decrease, not expected to be clinically relevant.

769 <sup>¶</sup>The effect of other hormonal contraceptive preparations or hormone replacement therapy on the  
770 pharmacokinetics of lamotrigine has not been evaluated, although the effect may be similar.

771 <sup>#</sup>Modest decrease in levonorgestrel (see PRECAUTIONS: Drug Interactions: Effect of  
772 LAMICTAL on Oral Contraceptives).

773

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

775 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** No evidence of carcinogenicity  
776 was seen in 1 mouse study or 2 rat studies following oral administration of lamotrigine for up to  
777 2 years at maximum tolerated doses (30 mg/kg per day for mice and 10 to 15 mg/kg per day for  
778 rats, doses that are equivalent to 90 mg/m<sup>2</sup> and 60 to 90 mg/m<sup>2</sup>, respectively). Steady-state  
779 plasma concentrations ranged from 1 to 4 mcg/mL in the mouse study and 1 to 10 mcg/mL in the  
780 rat study. Plasma concentrations associated with the recommended human doses of 300 to  
781 500 mg/day are generally in the range of 2 to 5 mcg/mL, but concentrations as high as  
782 19 mcg/mL have been recorded.

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

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

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

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

807 Lamotrigine did not affect fertility, teratogenesis, or postnatal development when rats were  
808 dosed prior to and during mating, and throughout gestation and lactation at doses equivalent to  
809 0.4 times the highest usual human maintenance dose on a mg/m<sup>2</sup> basis.

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

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

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

829 **Pregnancy Exposure Registry:** To facilitate monitoring fetal outcomes of pregnant women  
830 exposed to lamotrigine, physicians are encouraged to register patients, **before fetal outcome**

831 (e.g., ultrasound, results of amniocentesis, birth, etc.) is known, and can obtain information  
832 by calling the Lamotrigine Pregnancy Registry at (800) 336-2176 (toll-free). Patients can enroll  
833 themselves in the North American Antiepileptic Drug Pregnancy Registry by calling (888) 233-  
834 2334 (toll-free).

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

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

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

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

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

## 850 **ADVERSE REACTIONS**

851 **SERIOUS RASH REQUIRING HOSPITALIZATION AND DISCONTINUATION OF**  
852 **LAMICTAL, INCLUDING STEVENS-JOHNSON SYNDROME AND TOXIC**  
853 **EPIDERMAL NECROLYSIS, HAVE OCCURRED IN ASSOCIATION WITH**  
854 **THERAPY WITH LAMICTAL. RARE DEATHS HAVE BEEN REPORTED, BUT**  
855 **THEIR NUMBERS ARE TOO FEW TO PERMIT A PRECISE ESTIMATE OF THE**  
856 **RATE (see BOX WARNING).**

### 857 **Epilepsy:**

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

859 ***Adults With Epilepsy:*** The most commonly observed ( $\geq 5\%$ ) adverse experiences seen in  
860 association with LAMICTAL during adjunctive therapy in adults and not seen at an equivalent  
861 frequency among placebo-treated patients were: dizziness, ataxia, somnolence, headache,  
862 diplopia, blurred vision, nausea, vomiting, and rash. Dizziness, diplopia, ataxia, blurred vision,  
863 nausea, and vomiting were dose related. Dizziness, diplopia, ataxia, and blurred vision occurred  
864 more commonly in patients receiving carbamazepine with LAMICTAL than in patients receiving  
865 other AEDs with LAMICTAL. Clinical data suggest a higher incidence of rash, including serious  
866 rash, in patients receiving concomitant valproate than in patients not receiving valproate (see  
867 WARNINGS).

868 Approximately 11% of the 3,378 adult patients who received LAMICTAL as adjunctive  
869 therapy in premarketing clinical trials discontinued treatment because of an adverse experience.

870 The adverse events most commonly associated with discontinuation were rash (3.0%), dizziness  
871 (2.8%), and headache (2.5%).

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

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

884 Approximately 10% of the 420 adult patients who received LAMICTAL as monotherapy in  
885 premarketing clinical trials discontinued treatment because of an adverse experience. The  
886 adverse events most commonly associated with discontinuation were rash (4.5%), headache  
887 (3.1%), and asthenia (2.4%).

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

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

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

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

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

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

Body System/ Adverse Experience <sup>†</sup>	Percent of Patients Receiving Adjunctive LAMICTAL (n = 711)	Percent of Patients Receiving Adjunctive Placebo (n = 419)
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

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

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

924  
925 In a randomized, parallel study comparing placebo and 300 and 500 mg/day of LAMICTAL,  
926 some of the more common drug-related adverse events were dose related (see Table 5).

927

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

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

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

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

932

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

936 The overall adverse experience profile for LAMICTAL was similar between females and  
 937 males, and was independent of age. Because the largest non-Caucasian racial subgroup was only  
 938 6% of patients exposed to LAMICTAL in placebo-controlled trials, there are insufficient data to  
 939 support a statement regarding the distribution of adverse experience reports by race. Generally,  
 940 females receiving either adjunctive LAMICTAL or placebo were more likely to report adverse  
 941 experiences than males. The only adverse experience for which the reports on LAMICTAL were  
 942 greater than 10% more frequent in females than males (without a corresponding difference by  
 943 gender on placebo) was dizziness (difference = 16.5%). There was little difference between  
 944 females and males in the rates of discontinuation of LAMICTAL for individual adverse  
 945 experiences.

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

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

951

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

Body System/ Adverse Experience <sup>†</sup>	Percent of Patients Receiving LAMICTAL Monotherapy <sup>‡</sup> (n = 43)	Percent of Patients Receiving Low-Dose Valproate <sup>§</sup> 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

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

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

960 ‡ Up to 500 mg/day.

961 § 1,000 mg/day.

962

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

965 **Body as a Whole:** Asthenia, fever.  
 966 **Digestive:** Anorexia, dry mouth, rectal hemorrhage, peptic ulcer.  
 967 **Metabolic and Nutritional:** Peripheral edema.  
 968 **Nervous System:** Amnesia, ataxia, depression, hypesthesia, libido increase, decreased  
 969 reflexes, increased reflexes, nystagmus, irritability, suicidal ideation.  
 970 **Respiratory:** Epistaxis, bronchitis, dyspnea.  
 971 **Skin and Appendages:** Contact dermatitis, dry skin, sweating.  
 972 **Special Senses:** Vision abnormality.  
 973 **Incidence in Controlled Adjunctive Trials in Pediatric Patients With Epilepsy:**  
 974 Table 7 lists adverse events that occurred in at least 2% of 339 pediatric patients who received  
 975 LAMICTAL up to 15 mg/kg per day or a maximum of 750 mg per day. Reported adverse events  
 976 were classified using COSTART terminology.  
 977  
 978 **Table 7. Treatment-Emergent Adverse Event Incidence in Placebo-Controlled Adjunctive**  
 979 **Trials in Pediatric Patients With Epilepsy (Events in at least 2% of patients treated with**  
 980 **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

981  
982 **Bipolar Disorder:** The most commonly observed ( $\geq 5\%$ ) adverse experiences seen in  
983 association with the use of LAMICTAL as monotherapy (100 to 400 mg/day) in Bipolar  
984 Disorder in the 2 double-blind, placebo-controlled trials of 18 months' duration, and numerically  
985 more frequent than in placebo-treated patients are included in Table 8. Adverse events that  
986 occurred in at least 5% of patients and were numerically more common during the dose  
987 escalation phase of LAMICTAL in these trials (when patients may have been receiving  
988 concomitant medications) compared to the monotherapy phase were: headache (25%), rash  
989 (11%), dizziness (10%), diarrhea (8%), dream abnormality (6%), and pruritus (6%).

990 During the monotherapy phase of the double-blind, placebo-controlled trials of 18 months'  
991 duration, 13% of 227 patients who received LAMICTAL (100 to 400 mg/day), 16% of  
992 190 patients who received placebo, and 23% of 166 patients who received lithium discontinued  
993 therapy because of an adverse experience. The adverse events which most commonly led to  
994 discontinuation of LAMICTAL were rash (3%) and mania/hypomania/mixed mood adverse  
995 events (2%). Approximately 16% of 2,401 patients who received LAMICTAL (50 to  
996 500 mg/day) for Bipolar Disorder in premarketing trials discontinued therapy because of an  
997 adverse experience; most commonly due to rash (5%) and mania/hypomania/mixed mood  
998 adverse events (2%).

999 ***Incidence in Controlled Clinical Studies of LAMICTAL for the Maintenance***  
1000 ***Treatment of Bipolar I Disorder:*** Table 8 lists treatment-emergent signs and symptoms that  
1001 occurred in at least 5% of patients with Bipolar Disorder treated with LAMICTAL monotherapy  
1002 (100 to 400 mg/day), following the discontinuation of other psychotropic drugs, in  
1003 2 double-blind, placebo-controlled trials of 18 months' duration and were numerically more  
1004 frequent than in the placebo group.

1006 **Table 8. Treatment-Emergent Adverse Event Incidence in 2 Placebo-Controlled Trials**  
 1007 **in Adults With Bipolar I Disorder\* (Events in at least 5% of patients treated with**  
 1008 **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

1009 \* Patients in these studies were converted to LAMICTAL (100 to 400 mg/day) or placebo  
 1010 monotherapy from add-on therapy with other psychotropic medications. Patients may  
 1011 have reported multiple adverse experiences during the study; thus, patients may be  
 1012 included in more than one category.

1013 † Adverse experiences reported by at least 5% of patients are included.

1014 ‡ In the overall bipolar and other mood disorders clinical trials, the rate of serious rash  
 1015 was 0.08% (1 of 1,233) of adult patients who received LAMICTAL as initial  
 1016 monotherapy and 0.13% (2 of 1,538) of adult patients who received LAMICTAL as  
 1017 adjunctive therapy (see WARNINGS).

1018  
 1019 These adverse events were usually mild to moderate in intensity.

1020 Other events that occurred in 5% or more patients but equally or more frequently in the  
 1021 placebo group included: dizziness, mania, headache, infection, influenza, pain, accidental injury,  
 1022 diarrhea, and dyspepsia.

1023 Adverse events that occurred with a frequency of less than 5% and greater than 1% of patients  
 1024 receiving LAMICTAL and numerically more frequent than placebo were:

1025 **General:** Fever, neck pain.  
1026 **Cardiovascular:** Migraine.  
1027 **Digestive:** Flatulence.  
1028 **Metabolic and Nutritional:** Weight gain, edema.  
1029 **Musculoskeletal:** Arthralgia, myalgia.  
1030 **Nervous System:** Amnesia, depression, agitation, emotional lability, dyspraxia, abnormal  
1031 thoughts, dream abnormality, hypoesthesia.  
1032 **Respiratory:** Sinusitis.  
1033 **Urogenital:** Urinary frequency.  
1034 **Adverse Events Following Abrupt Discontinuation:** In the 2 maintenance trials, there  
1035 was no increase in the incidence, severity or type of adverse events in Bipolar Disorder patients  
1036 after abruptly terminating LAMICTAL therapy. In clinical trials in patients with Bipolar  
1037 Disorder, 2 patients experienced seizures shortly after abrupt withdrawal of LAMICTAL.  
1038 However, there were confounding factors that may have contributed to the occurrence of seizures  
1039 in these bipolar patients (see DOSAGE AND ADMINISTRATION).  
1040 **Mania/Hypomania/Mixed Episodes:** During the double-blind, placebo-controlled clinical  
1041 trials in Bipolar I Disorder in which patients were converted to LAMICTAL monotherapy (100  
1042 to 400 mg/day) from other psychotropic medications and followed for durations up to 18 months,  
1043 the rate of manic or hypomanic or mixed mood episodes reported as adverse experiences was 5%  
1044 for patients treated with LAMICTAL (n = 227), 4% for patients treated with lithium (n = 166),  
1045 and 7% for patients treated with placebo (n = 190). In all bipolar controlled trials combined,  
1046 adverse events of mania (including hypomania and mixed mood episodes) were reported in 5%  
1047 of patients treated with LAMICTAL (n = 956), 3% of patients treated with lithium (n = 280), and  
1048 4% of patients treated with placebo (n = 803).  
1049 The overall adverse event profile for LAMICTAL was similar between females and males,  
1050 between elderly and nonelderly patients, and among racial groups.  
1051 **Other Adverse Events Observed During All Clinical Trials For Pediatric and Adult**  
1052 **Patients With Epilepsy or Bipolar Disorder and Other Mood Disorders:** LAMICTAL  
1053 has been administered to 6,694 individuals for whom complete adverse event data was captured  
1054 during all clinical trials, only some of which were placebo controlled. During these trials, all  
1055 adverse events were recorded by the clinical investigators using terminology of their own  
1056 choosing. To provide a meaningful estimate of the proportion of individuals having adverse  
1057 events, similar types of events were grouped into a smaller number of standardized categories  
1058 using modified COSTART dictionary terminology. The frequencies presented represent the  
1059 proportion of the 6,694 individuals exposed to LAMICTAL who experienced an event of the  
1060 type cited on at least one occasion while receiving LAMICTAL. All reported events are included  
1061 except those already listed in the previous tables or elsewhere in the labeling, those too general  
1062 to be informative, and those not reasonably associated with the use of the drug.  
1063 Events are further classified within body system categories and enumerated in order of  
1064 decreasing frequency using the following definitions: *frequent* adverse events are defined as

1065 those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100  
1066 to 1/1,000 patients; *rare* adverse events are those occurring in fewer than 1/1,000 patients.

1067 **Body as a Whole: Infrequent:** Allergic reaction, chills, halitosis, and malaise. **Rare:**  
1068 Abdomen enlarged, abscess, and suicide/suicide attempt.

1069 **Cardiovascular System: Infrequent:** Flushing, hot flashes, hypertension, palpitations,  
1070 postural hypotension, syncope, tachycardia, and vasodilation. **Rare:** Angina pectoris, atrial  
1071 fibrillation, deep thrombophlebitis, ECG abnormality, and myocardial infarction.

1072 **Dermatological: Infrequent:** Acne, alopecia, hirsutism, maculopapular rash, skin  
1073 discoloration, and urticaria. **Rare:** Angioedema, erythema, exfoliative dermatitis, fungal  
1074 dermatitis, herpes zoster, leukoderma, multiforme erythema, petechial rash, pustular rash,  
1075 seborrhea, Stevens-Johnson syndrome, and vesiculobullous rash.

1076 **Digestive System: Infrequent:** Dysphagia, eructation, gastritis, gingivitis, increased  
1077 appetite, increased salivation, liver function tests abnormal, and mouth ulceration. **Rare:**  
1078 Gastrointestinal hemorrhage, glossitis, gum hemorrhage, gum hyperplasia, hematemesis,  
1079 hemorrhagic colitis, hepatitis, melena, stomach ulcer, stomatitis, thirst, and tongue edema.

1080 **Endocrine System: Rare:** Goiter and hypothyroidism.

1081 **Hematologic and Lymphatic System: Infrequent:** Ecchymosis and leukopenia. **Rare:**  
1082 Anemia, eosinophilia, fibrin decrease, fibrinogen decrease, iron deficiency anemia, leukocytosis,  
1083 lymphocytosis, macrocytic anemia, petechia, and thrombocytopenia.

1084 **Metabolic and Nutritional Disorders: Infrequent:** Aspartate transaminase increased.  
1085 **Rare:** Alcohol intolerance, alkaline phosphatase increase, alanine transaminase increase,  
1086 bilirubinemia, general edema, gamma glutamyl transpeptidase increase, and hyperglycemia.

1087 **Musculoskeletal System: Infrequent:** Arthritis, leg cramps, myasthenia, and twitching.  
1088 **Rare:** Bursitis, joint disorder, muscle atrophy, pathological fracture, and tendinous contracture.

1089 **Nervous System: Frequent:** Confusion and paresthesia. **Infrequent:** Akathisia, apathy,  
1090 aphasia, CNS depression, depersonalization, dysarthria, dyskinesia, euphoria, hallucinations,  
1091 hostility, hyperkinesia, hypertonia, libido decreased, memory decrease, mind racing, movement  
1092 disorder, myoclonus, panic attack, paranoid reaction, personality disorder, psychosis, sleep  
1093 disorder, stupor, and suicidal ideation. **Rare:** Cerebellar syndrome, cerebrovascular accident,  
1094 cerebral sinus thrombosis, choreoathetosis, CNS stimulation, delirium, delusions, dysphoria,  
1095 dystonia, extrapyramidal syndrome, faintness, grand mal convulsions, hemiplegia, hyperalgesia,  
1096 hyperesthesia, hypokinesia, hypotonia, manic depression reaction, muscle spasm, neuralgia,  
1097 neurosis, paralysis, and peripheral neuritis.

1098 **Respiratory System: Infrequent:** Yawn. **Rare:** Hiccup and hyperventilation.

1099 **Special Senses: Frequent:** Amblyopia. **Infrequent:** Abnormality of accommodation,  
1100 conjunctivitis, dry eyes, ear pain, photophobia, taste perversion, and tinnitus. **Rare:** Deafness,  
1101 lacrimation disorder, oscillopsia, parosmia, ptosis, strabismus, taste loss, uveitis, and visual field  
1102 defect.

1103 **Urogenital System: Infrequent:** Abnormal ejaculation, breast pain, hematuria, impotence,  
1104 menorrhagia, polyuria, urinary incontinence, and urine abnormality. **Rare:** Acute kidney failure,

1105 anorgasmia, breast abscess, breast neoplasm, creatinine increase, cystitis, dysuria, epididymitis,  
1106 female lactation, kidney failure, kidney pain, nocturia, urinary retention, urinary urgency, and  
1107 vaginal moniliasis.

1108 **Postmarketing and Other Experience:** In addition to the adverse experiences reported  
1109 during clinical testing of LAMICTAL, the following adverse experiences have been reported in  
1110 patients receiving marketed LAMICTAL and from worldwide noncontrolled investigational use.  
1111 These adverse experiences have not been listed above, and data are insufficient to support an  
1112 estimate of their incidence or to establish causation.

1113 **Blood and Lymphatic:** Agranulocytosis, aplastic anemia, disseminated intravascular  
1114 coagulation, hemolytic anemia, neutropenia, pancytopenia, red cell aplasia.

1115 **Gastrointestinal:** Esophagitis.

1116 **Hepatobiliary Tract and Pancreas:** Pancreatitis.

1117 **Immunologic:** Lupus-like reaction, vasculitis.

1118 **Lower Respiratory:** Apnea.

1119 **Musculoskeletal:** Rhabdomyolysis has been observed in patients experiencing  
1120 hypersensitivity reactions.

1121 **Neurology:** Exacerbation of parkinsonian symptoms in patients with pre-existing  
1122 Parkinson's disease, tics.

1123 **Non-site Specific:** Hypersensitivity reaction, multiorgan failure, progressive  
1124 immunosuppression.

## 1125 **DRUG ABUSE AND DEPENDENCE**

1126 The abuse and dependence potential of LAMICTAL have not been evaluated in human  
1127 studies.

## 1128 **OVERDOSAGE**

1129 **Human Overdose Experience:** Overdoses involving quantities up to 15 g have been  
1130 reported for LAMICTAL, some of which have been fatal. Overdose has resulted in ataxia,  
1131 nystagmus, increased seizures, decreased level of consciousness, coma, and intraventricular  
1132 conduction delay.

1133 **Management of Overdose:** There are no specific antidotes for LAMICTAL. Following a  
1134 suspected overdose, hospitalization of the patient is advised. General supportive care is  
1135 indicated, including frequent monitoring of vital signs and close observation of the patient. If  
1136 indicated, emesis should be induced or gastric lavage should be performed; usual precautions  
1137 should be taken to protect the airway. It should be kept in mind that lamotrigine is rapidly  
1138 absorbed (see CLINICAL PHARMACOLOGY). It is uncertain whether hemodialysis is an  
1139 effective means of removing lamotrigine from the blood. In 6 renal failure patients, about 20% of  
1140 the amount of lamotrigine in the body was removed by hemodialysis during a 4-hour session. A  
1141 Poison Control Center should be contacted for information on the management of overdosage of  
1142 LAMICTAL.

1143 **DOSAGE AND ADMINISTRATION**

1144 **Epilepsy:**

1145 **Adjunctive Use:** LAMICTAL is indicated as adjunctive therapy for partial seizures in  
1146 adults and pediatric patients ( $\geq 2$  years of age). LAMICTAL is also indicated as adjunctive  
1147 therapy for the generalized seizures of Lennox-Gastaut syndrome in adult and pediatric patients  
1148 ( $\geq 2$  years of age).

1149 **Monotherapy Use:** LAMICTAL is indicated for conversion to monotherapy in adults with  
1150 partial seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital,  
1151 primidone, or valproate as the single AED.

1152 **Safety and effectiveness of LAMICTAL have not been established (1) as initial**  
1153 **monotherapy, (2) for conversion to monotherapy from AEDs other than carbamazepine,**  
1154 **phenytoin, phenobarbital, primidone, or valproate, or (3) for simultaneous conversion to**  
1155 **monotherapy from 2 or more concomitant AEDs.**

1156 **Safety and effectiveness in pediatric patients below the age of 16 years other than those**  
1157 **with partial seizures and the generalized seizures of Lennox-Gastaut syndrome have not**  
1158 **been established (see BOX WARNING).**

1159 **Bipolar Disorder:** LAMICTAL is indicated for the maintenance treatment of Bipolar I  
1160 Disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania,  
1161 mixed episodes) in patients treated for acute mood episodes with standard therapy. The  
1162 effectiveness of LAMICTAL in the acute treatment of mood episodes has not been established.

1163 **General Dosing Considerations for Epilepsy and Bipolar Disorder Patients:** The  
1164 risk of nonserious rash is increased when the recommended initial dose and/or the rate of dose  
1165 escalation of LAMICTAL is exceeded. There are suggestions, yet to be proven, that the risk of  
1166 severe, potentially life-threatening rash may be increased by (1) coadministration of LAMICTAL  
1167 with valproate, (2) exceeding the recommended initial dose of LAMICTAL, or (3) exceeding the  
1168 recommended dose escalation for LAMICTAL. However, cases have been reported in the  
1169 absence of these factors (see BOX WARNING). Therefore, it is important that the dosing  
1170 recommendations be followed closely.

1171 It is recommended that LAMICTAL not be restarted in patients who discontinued due to rash  
1172 associated with prior treatment with LAMICTAL, unless the potential benefits clearly outweigh  
1173 the risks. If the decision is made to restart a patient who has discontinued LAMICTAL, the need  
1174 to restart with the initial dosing recommendations should be assessed. The greater the interval of  
1175 time since the previous dose, the greater consideration should be given to restarting with the  
1176 initial dosing recommendations. If a patient has discontinued LAMICTAL for a period of more  
1177 than 5 half-lives, it is recommended that initial dosing recommendations and guidelines be  
1178 followed. The half-life of LAMICTAL is affected by other concomitant medications (see  
1179 CLINICAL PHARMACOLOGY: Pharmacokinetics and Drug Metabolism).

1180 **Women and Oral Contraceptives: Starting LAMICTAL in Women Taking Oral**

1181 **Contraceptives:** Although oral contraceptives have been shown to increase the clearance of  
1182 lamotrigine (see PRECAUTIONS: Drug Interactions), no adjustments to the recommended dose

1183 escalation guidelines for LAMICTAL should be necessary solely based on the use of oral  
1184 contraceptives. Therefore, dose escalation should follow the recommended guidelines based on  
1185 whether LAMICTAL is added to valproate, whether LAMICTAL is added to carbamazepine,  
1186 phenytoin, phenobarbital, primidone, or rifampin, or whether LAMICTAL is added in the  
1187 absence of valproate, carbamazepine, phenytoin, phenobarbital, primidone, or rifampin.

1188 ***Adjustments to the Maintenance Dose of LAMICTAL: (1) Taking or Starting***

1189 ***Oral Contraceptives:*** For women not taking carbamazepine, phenytoin, phenobarbital,  
1190 primidone, or rifampin, the maintenance dose of LAMICTAL may need to be increased, by as  
1191 much as 2 fold over the recommended target maintenance dose, according to clinical response  
1192 (see PRECAUTIONS: Drug Interactions). For women taking LAMICTAL in addition to  
1193 carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, no adjustment should be  
1194 necessary. ***(2) Stopping Oral Contraceptives:*** For women not taking carbamazepine,  
1195 phenytoin, phenobarbital, primidone, or rifampin, the maintenance dose of LAMICTAL may  
1196 need to be decreased by as much as 50% of the maintenance dose with concurrent oral  
1197 contraceptives, according to clinical response (see PRECAUTIONS: Drug Interactions). For  
1198 women taking LAMICTAL in addition to carbamazepine, phenytoin, phenobarbital, primidone  
1199 or rifampin, no adjustment should be necessary.

1200 ***Women and Other Hormonal Contraceptive Preparations or Hormone***

1201 ***Replacement Therapy:*** Although the effect of other hormonal contraceptive preparations or  
1202 hormone replacement therapy on the pharmacokinetics of lamotrigine has not been evaluated, the  
1203 effect may be similar to oral contraceptives (see PRECAUTIONS: Drug Interactions). Therefore,  
1204 similar adjustments to the dosage of LAMICTAL may be needed, based on clinical response.

1205 ***Patients With Hepatic Impairment:*** Experience in patients with hepatic impairment is  
1206 limited. Based on a clinical pharmacology study in 24 patients with moderate to severe liver  
1207 dysfunction (see CLINICAL PHARMACOLOGY), the following general recommendations can  
1208 be made. Initial, escalation, and maintenance doses should generally be reduced by  
1209 approximately 50% in patients with moderate (Child-Pugh Grade B) and 75% in patients with  
1210 severe (Child-Pugh Grade C) hepatic impairment. Escalation and maintenance doses should be  
1211 adjusted according to clinical response.

1212 ***Patients With Renal Functional Impairment:*** Initial doses of LAMICTAL should be  
1213 based on patients' AED regimen (see above); reduced maintenance doses may be effective for  
1214 patients with significant renal functional impairment (see CLINICAL PHARMACOLOGY).  
1215 Few patients with severe renal impairment have been evaluated during chronic treatment with  
1216 LAMICTAL. Because there is inadequate experience in this population, LAMICTAL should be  
1217 used with caution in these patients.

1218 ***Epilepsy:***

1219 ***Adjunctive Therapy With LAMICTAL for Epilepsy:*** This section provides specific  
1220 dosing recommendations for patients 2 to 12 years of age and patients greater than 12 years of  
1221 age. Within each of these age-groups, specific dosing recommendations are provided depending  
1222 upon whether or not the patient is receiving valproate (Tables 9 and 10 for patients 2 to 12 years

1223 of age, Tables 11 and 12 for patients greater than 12 years of age). In addition, the section  
1224 provides a discussion of dosing for those patients receiving concomitant AEDs that have not  
1225 been systematically evaluated in combination with LAMICTAL.

1226 ***Patients 2 to 12 Years of Age: LAMICTAL Added to an Antiepileptic Drug***  
1227 ***Regimen Containing Valproate:*** Recommended dosing guidelines are summarized in  
1228 Table 9.

1229 ***LAMICTAL Added to Carbamazepine, Phenytoin, Phenobarbital, or***  
1230 ***Primidone:*** Recommended dosing guidelines are summarized in Table 10.

1231 ***LAMICTAL Added to Oxcarbazepine or Levetiracetam, or to Antiepileptic***  
1232 ***Drugs for Which the Interaction With Lamotrigine is Not Known:*** Oxcarbazepine and  
1233 levetiracetam do not affect the apparent clearance of lamotrigine. Specific dosing guidelines for  
1234 the addition of LAMICTAL to oxcarbazepine or levetiracetam have not been studied in clinical  
1235 trials. The effect of AEDs other than those already specified on the metabolism of LAMICTAL  
1236 is not currently known. Therefore, no specific dosing guidelines can be provided. Conservative  
1237 starting doses and dose escalations (as with concomitant valproate) would be prudent;  
1238 maintenance dosing would be expected to fall between the maintenance dose with valproate,  
1239 which decreases the apparent clearance of lamotrigine, and the maintenance dose without  
1240 valproate, but with carbamazepine, phenytoin, phenobarbital, or primidone, which increase the  
1241 apparent clearance of lamotrigine.

1242 Note that the starting doses and dose escalations listed in Tables 9 and 10 are different than  
1243 those used in clinical trials; however, the maintenance doses are the same as in clinical trials.  
1244 Smaller starting doses and slower dose escalations than those used in clinical trials are  
1245 recommended because of the suggestions that the risk of rash may be decreased by smaller  
1246 starting doses and slower dose escalations. Therefore, maintenance doses will take longer to  
1247 reach in clinical practice than in clinical trials. It may take several weeks to months to achieve an  
1248 individualized maintenance dose. Maintenance doses in patients weighing less than 30 kg,  
1249 regardless of age or concomitant AED, may need to be increased as much as 50%, based on  
1250 clinical response.

1251 **The smallest available strength of LAMICTAL Chewable Dispersible Tablets is 2 mg,**  
1252 **and only whole tablets should be administered. If the calculated dose cannot be achieved**  
1253 **using whole tablets, the dose should be rounded down to the nearest whole tablet (see**  
1254 **HOW SUPPLIED and PATIENT INFORMATION for a description of the available sizes**  
1255 **of LAMICTAL Chewable Dispersible Tablets).**

1256

1257 **Table 9. LAMICTAL Added to an Antiepileptic Regimen Containing Valproate in Patients**  
 1258 **2 to 12 Years of Age**

Weeks 1 and 2		0.15 mg/kg/day in 1 or 2 divided doses, rounded down to the nearest whole tablet. Only whole tablets should be used for dosing.	
Weeks 3 and 4		0.3 mg/kg/day in 1 or 2 divided doses, rounded down to the nearest whole tablet.	
Weight based dosing can be achieved by using the following guide:			
If the patient's weight is		Give this daily dose, using the most appropriate combination of LAMICTAL 2-mg and 5-mg tablets	
Greater than	And less than	Weeks 1 and 2	Weeks 3 and 4
6.7 kg	14 kg	2 mg every <i>other</i> day	2 mg every day
14.1 kg	27 kg	2 mg every day	4 mg every day
27.1 kg	34 kg	4 mg every day	8 mg every day
34.1 kg	40 kg	5 mg every day	10 mg every day
<p>Usual maintenance dose: 1 to 5 mg/kg/day (maximum 200 mg/day in 1 or 2 divided doses). To achieve the usual maintenance dose, subsequent doses should be increased every 1 to 2 weeks as follows: calculate 0.3 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily dose. The usual maintenance dose in patients adding LAMICTAL to valproate alone ranges from 1 to 3 mg/kg/day. Maintenance doses in patients weighing less than 30 kg may need to be increased by as much as 50%, based on clinical response.</p>			

1259 **Table 10. LAMICTAL Added to Carbamazepine, Phenytoin, Phenobarbital, or**  
 1260 **Primidone\* (Without Valproate) in Patients 2 to 12 Years of Age**  
 1261

Weeks 1 and 2		0.6 mg/kg/day in 2 divided doses, rounded down to the nearest whole tablet.	
Weeks 3 and 4		1.2 mg/kg/day in 2 divided doses, rounded down to the nearest whole tablet.	
<p>Usual maintenance dose: 5 to 15 mg/kg/day (maximum 400 mg/day in 2 divided doses). To achieve the usual maintenance dose, subsequent doses should be increased every 1 to 2 weeks as follows: calculate 1.2 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily dose. Maintenance doses in patients weighing less than 30 kg may need to be increased by as much as 50%, based on clinical response.</p>			

1262 \* Rifampin has also been shown to increase the apparent clearance of lamotrigine (see  
 1263 PRECAUTIONS: Drug Interactions).  
 1264

1265 **Patients Over 12 Years of Age: LAMICTAL Added to an Antiepileptic Drug**  
1266 **Regimen Containing Valproate:** Recommended dosing guidelines are summarized in  
1267 Table 11.

1268 **LAMICTAL Added to Carbamazepine, Phenytoin, Phenobarbital, or**  
1269 **Primidone:** Recommended dosing guidelines are summarized in Table 12.

1270 **LAMICTAL Added to Oxcarbazepine or Levetiracetam, or to Antiepileptic**  
1271 **Drugs for Which the Interaction With Lamotrigine is Not Known:** Oxcarbazepine and  
1272 levetiracetam do not affect the apparent clearance of lamotrigine. Specific dosing guidelines for  
1273 the addition of LAMICTAL to oxcarbazepine or levetiracetam have not been studied in clinical  
1274 trials. The effect of AEDs other than those already specified on the metabolism of LAMICTAL  
1275 is not currently known. Therefore, no specific dosing guidelines can be provided. Conservative  
1276 starting doses and dose escalations (as with concomitant valproate) would be prudent;  
1277 maintenance dosing would be expected to fall between the maintenance dose with valproate,  
1278 which decreases the apparent clearance of lamotrigine, and the maintenance dose without  
1279 valproate, but with carbamazepine, phenytoin, phenobarbital, or primidone, which increase the  
1280 apparent clearance of lamotrigine.

1281  
1282 **Table 11. LAMICTAL Added to an Antiepileptic Drug Regimen Containing Valproate in**  
1283 **Patients Over 12 Years of Age**

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

1284  
1285 **Table 12. LAMICTAL Added to Carbamazepine, Phenytoin, Phenobarbital, or**  
1286 **Primidone\* (Without Valproate) in Patients Over 12 Years of Age**

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

1287 \* Rifampin has also been shown to increase the apparent clearance of lamotrigine (see  
1288 PRECAUTIONS: Drug Interactions).

1289  
1290 **Conversion From Adjunctive Therapy With Carbamazepine, Phenytoin,**  
1291 **Phenobarbital, Primidone, or Valproate as the Single AED to Monotherapy With**  
1292 **LAMICTAL in Patients  $\geq 16$  Years of Age With Epilepsy:** The goal of the transition  
1293 regimen is to effect the conversion to monotherapy with LAMICTAL under conditions that  
1294 ensure adequate seizure control while mitigating the risk of serious rash associated with the rapid  
1295 titration of LAMICTAL.

1296 The recommended maintenance dose of LAMICTAL as monotherapy is 500 mg/day given in  
1297 2 divided doses.

1298 To avoid an increased risk of rash, the recommended initial dose and subsequent dose  
1299 escalations of LAMICTAL should not be exceeded (see BOX WARNING).

1300 **Conversion From Adjunctive Therapy With Carbamazepine, Phenytoin,**  
1301 **Phenobarbital, or Primidone to Monotherapy With LAMICTAL:** After achieving a dose  
1302 of 500 mg/day of LAMICTAL according to the guidelines in Table 12, the concomitant AED  
1303 should be withdrawn by 20% decrements each week over a 4-week period. The regimen for the  
1304 withdrawal of the concomitant AED is based on experience gained in the controlled  
1305 monotherapy clinical trial.

1306 **Conversion from Adjunctive Therapy With Valproate to Monotherapy With**  
1307 **LAMICTAL:** The conversion regimen involves 4 steps. First, achieve a dose of 200 mg/day of  
1308 LAMICTAL according to the guidelines in Table 11. Second, while keeping the LAMICTAL  
1309 dose at 200 mg/day, valproate should be gradually decreased to a dose of 500 mg/day by  
1310 decrements no greater than 500 mg/day per week. This dosage regimen is then maintained for  
1311 1 week. Third, LAMICTAL should then be increased to 300 mg/day while valproate is  
1312 simultaneously decreased to 250 mg/day. This regimen should be maintained for 1 week. Fourth,  
1313 valproate should then be discontinued completely and LAMICTAL increased by 100 mg/day  
1314 every week until the recommended monotherapy dose of 500 mg/day is reached (see Table 13).  
1315

1316 **Table 13. Conversion From Adjunctive Therapy With Valproate to Monotherapy With**  
1317 **LAMICTAL in Patients  $\geq 16$  Years of Age**

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

1318  
1319 **Conversion from Adjunctive Therapy With Antiepileptic Drugs Other Than**  
1320 **Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate to**  
1321 **Monotherapy With LAMICTAL:** No specific dosing guidelines can be provided for

1322 conversion to monotherapy with LAMICTAL with AEDs other than carbamazepine,  
1323 phenobarbital, phenytoin, primidone, or valproate.

1324 **Usual Maintenance Dose for Epilepsy:** The usual maintenance doses identified in  
1325 Tables 9-12 are derived from dosing regimens employed in the placebo-controlled adjunctive  
1326 studies in which the efficacy of LAMICTAL was established. In patients receiving multidrug  
1327 regimens employing carbamazepine, phenytoin, phenobarbital, or primidone **without valproate**,  
1328 maintenance doses of adjunctive LAMICTAL as high as 700 mg/day have been used. In patients  
1329 receiving **valproate alone**, maintenance doses of adjunctive LAMICTAL as high as 200 mg/day  
1330 have been used. The advantage of using doses above those recommended in Tables 9-13 has not  
1331 been established in controlled trials.

1332 **Discontinuation Strategy for Patients With Epilepsy:** For patients receiving  
1333 LAMICTAL in combination with other AEDs, a reevaluation of all AEDs in the regimen should  
1334 be considered if a change in seizure control or an appearance or worsening of adverse  
1335 experiences is observed.

1336 If a decision is made to discontinue therapy with LAMICTAL, a step-wise reduction of dose  
1337 over at least 2 weeks (approximately 50% per week) is recommended unless safety concerns  
1338 require a more rapid withdrawal (see PRECAUTIONS).

1339 *Discontinuing carbamazepine, phenytoin, phenobarbital, or primidone should prolong the*  
1340 *half-life of lamotrigine; discontinuing valproate should shorten the half-life of lamotrigine.*

1341 **Target Plasma Levels for Patients With Epilepsy:** A therapeutic plasma concentration  
1342 range has not been established for lamotrigine. Dosing of LAMICTAL should be based on  
1343 therapeutic response.

1344 **Bipolar Disorder:** The goal of maintenance treatment with LAMICTAL is to delay the time to  
1345 occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated  
1346 for acute mood episodes with standard therapy. The target dose of LAMICTAL is 200 mg/day  
1347 (100 mg/day in patients taking valproate, which decreases the apparent clearance of lamotrigine,  
1348 and 400 mg/day in patients not taking valproate and taking either carbamazepine, phenytoin,  
1349 phenobarbital, primidone, or rifampin, which increase the apparent clearance of lamotrigine). In  
1350 the clinical trials, doses up to 400 mg/day as monotherapy were evaluated, however, no  
1351 additional benefit was seen at 400 mg/day compared to 200 mg/day (see CLINICAL STUDIES:  
1352 Bipolar Disorder). Accordingly, doses above 200 mg/day are not recommended. Treatment with  
1353 LAMICTAL is introduced, based on concurrent medications, according to the regimen outlined  
1354 in Table 14. If other psychotropic medications are withdrawn following stabilization, the dose of  
1355 LAMICTAL should be adjusted. For patients discontinuing valproate, the dose of LAMICTAL  
1356 should be doubled over a 2-week period in equal weekly increments (see Table 15). For patients  
1357 discontinuing carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, the dose of  
1358 LAMICTAL should remain constant for the first week and then should be decreased by half over  
1359 a 2-week period in equal weekly decrements (see Table 15). The dose of LAMICTAL may then  
1360 be further adjusted to the target dose (200 mg) as clinically indicated.

1361 If other drugs are subsequently introduced, the dose of LAMICTAL may need to be adjusted.  
 1362 In particular, the introduction of valproate requires reduction in the dose of LAMICTAL (see  
 1363 CLINICAL PHARMACOLOGY: Drug Interactions).

1364 To avoid an increased risk of rash, the recommended initial dose and subsequent dose  
 1365 escalations of LAMICTAL should not be exceeded (see BOX WARNING).

1366

1367 **Table 14. Escalation Regimen for LAMICTAL for Patients With Bipolar Disorder\***

	For Patients Not Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Rifampin† and Not Taking Valproate‡	For Patients Taking Valproate‡	For Patients Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Rifampin† and Not Taking Valproate‡
Weeks 1 and 2	25 mg daily	25 mg every <i>other day</i>	50 mg daily
Weeks 3 and 4	50 mg daily	25 mg daily	100 mg daily, in divided doses
Week 5	100 mg daily	50 mg daily	200 mg daily, in divided doses
Week 6	200 mg daily	100 mg daily	300 mg daily, in divided doses
Week 7	200 mg daily	100 mg daily	up to 400 mg daily, in divided doses

1368 \*See CLINICAL PHARMACOLOGY: Drug Interactions and PRECAUTIONS: Drug  
 1369 Interactions for a description of known drug interactions.

1370 †Carbamazepine, phenytoin, phenobarbital, primidone, and rifampin have been shown to  
 1371 increase the apparent clearance of lamotrigine.

1372 ‡Valproate has been shown to decrease the apparent clearance of lamotrigine.

1373

1374 **Table 15. Adjustments to LAMICTAL Dosing for Patients With Bipolar Disorder**  
 1375 **Following Discontinuation of Psychotropic Medications\***

	Discontinuation of Psychotropic Drugs (excluding Carbamazepine, Phenytoin, Phenobarbital, Primidone, Rifampin <sup>†</sup> , or Valproate <sup>‡</sup> )	After Discontinuation of Valproate <sup>‡</sup>	After Discontinuation of Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Rifampin <sup>†</sup>
		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

1376 \*See CLINICAL PHARMACOLOGY: Drug Interactions and PRECAUTIONS: Drug  
 1377 Interactions for a description of known drug interactions.

1378 <sup>†</sup>Carbamazepine, phenytoin, phenobarbital, primidone, and rifampin have been shown to  
 1379 increase the apparent clearance of lamotrigine.

1380 <sup>‡</sup>Valproate has been shown to decrease the apparent clearance of lamotrigine.

1381  
 1382 There is no body of evidence available to answer the question of how long the patient should  
 1383 remain on LAMICTAL therapy. Systematic evaluation of the efficacy of LAMICTAL in patients  
 1384 with either depression or mania who responded to standard therapy during an acute 8 to 16 week  
 1385 treatment phase and were then randomized to LAMICTAL or placebo for up to 76 weeks of  
 1386 observation for affective relapse demonstrated a benefit of such maintenance treatment (see  
 1387 CLINICAL STUDIES: Bipolar Disorder). Nevertheless, patients should be periodically  
 1388 reassessed to determine the need for maintenance treatment.

1389 **Discontinuation Strategy in Bipolar Disorder:** As with other AEDs, LAMICTAL  
 1390 should not be abruptly discontinued. In the controlled clinical trials, there was no increase in the  
 1391 incidence, type, or severity of adverse experiences following abrupt termination of LAMICTAL.  
 1392 In clinical trials in patients with bipolar disorder, 2 patients experienced seizures shortly after  
 1393 abrupt withdrawal of LAMICTAL. However, there were confounding factors that may have  
 1394 contributed to the occurrence of seizures in these bipolar patients. Discontinuation of  
 1395 LAMICTAL should involve a step-wise reduction of dose over at least 2 weeks (approximately  
 1396 50% per week) unless safety concerns require a more rapid withdrawal.

1397 **Administration of LAMICTAL Chewable Dispersible Tablets:** LAMICTAL Chewable  
 1398 Dispersible Tablets may be swallowed whole, chewed, or dispersed in water or diluted fruit

1399 juice. If the tablets are chewed, consume a small amount of water or diluted fruit juice to aid in  
1400 swallowing.

1401 To disperse LAMICTAL Chewable Dispersible Tablets, add the tablets to a small amount of  
1402 liquid (1 teaspoon, or enough to cover the medication). Approximately 1 minute later, when the  
1403 tablets are completely dispersed, swirl the solution and consume the entire quantity immediately.  
1404 *No attempt should be made to administer partial quantities of the dispersed tablets.*

## 1405 **HOW SUPPLIED**

### 1406 **LAMICTAL Tablets, 25-mg**

1407 White, scored, shield-shaped tablets debossed with "LAMICTAL" and "25", bottles of 100  
1408 (NDC 0173-0633-02).

1409 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled**  
1410 **Room Temperature] in a dry place.**

### 1411 **LAMICTAL Tablets, 100-mg**

1412 Peach, scored, shield-shaped tablets debossed with "LAMICTAL" and "100", bottles of 100  
1413 (NDC 0173-0642-55).

### 1414 **LAMICTAL Tablets, 150-mg**

1415 Cream, scored, shield-shaped tablets debossed with "LAMICTAL" and "150", bottles of 60  
1416 (NDC 0173-0643-60).

### 1417 **LAMICTAL Tablets, 200-mg**

1418 Blue, scored, shield-shaped tablets debossed with "LAMICTAL" and "200", bottles of 60  
1419 (NDC 0173-0644-60).

1420 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled**  
1421 **Room Temperature] in a dry place and protect from light.**

1422

### 1423 **LAMICTAL Chewable Dispersible Tablets, 2-mg**

1424 White to off-white, round tablets debossed with "LTG" over "2", bottles of 30 (NDC 0173-  
1425 0699-00). ORDER DIRECTLY FROM GlaxoSmithKline 1-800-334-4153.

### 1426 **LAMICTAL Chewable Dispersible Tablets, 5-mg**

1427 White to off-white, caplet-shaped tablets debossed with "GX CL2", bottles of 100 (NDC  
1428 0173-0526-00).

### 1429 **LAMICTAL Chewable Dispersible Tablets, 25-mg**

1430 White, super elliptical-shaped tablets debossed with "GX CL5", bottles of 100 (NDC 0173-  
1431 0527-00).

1432 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled**  
1433 **Room Temperature] in a dry place.**

1434

### 1435 **LAMICTAL Starter Kit for Patients Taking Valproate**

1436 **25-mg**, white, scored, shield-shaped tablets debossed with "LAMICTAL" and "25",  
1437 blisterpack of 35 tablets (NDC 0173-0633-10).

1438 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled**  
1439 **Room Temperature] in a dry place.**

1440  
1441 **LAMICTAL Starter Kit for Patients Taking Carbamazepine, Phenytoin, Phenobarbital,**  
1442 **Primidone, or Rifampin and Not Taking Valproate**

1443 **25-mg**, white, scored, shield-shaped tablets debossed with "LAMICTAL" and "25" and  
1444 **100-mg**, peach, scored, shield-shaped tablets debossed with "LAMICTAL" and "100",  
1445 blisterpack of 84, 25-mg tablets and 14, 100-mg tablets (NDC 0173-0594-01)

1446 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled**  
1447 **Room Temperature] in a dry place and protect from light.**

1448  
1449 **LAMICTAL Starter Kit for Patients Not Taking Carbamazepine, Phenytoin,**  
1450 **Phenobarbital, Primidone, Rifampin, or Valproate**  
1451 **[FOR USE IN BIPOLAR PATIENTS ONLY]**

1452 **25-mg**, white, scored, shield-shaped tablets debossed with "LAMICTAL" and "25" and  
1453 **100-mg**, peach, scored, shield-shaped tablets debossed with "LAMICTAL" and "100",  
1454 blisterpack of 42, 25-mg tablets and 7, 100-mg tablets (NDC 0173-0594-02).

1455 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled**  
1456 **Room Temperature] in a dry place and protect from light.**

## 1457 **PATIENT INFORMATION**

1458 The following wording is contained in a separate leaflet provided for patients.

### 1459 **Information for the Patient**

#### 1460 **LAMICTAL<sup>®</sup> (lamotrigine) Tablets**

#### 1461 **LAMICTAL<sup>®</sup> (lamotrigine) Chewable Dispersible Tablets**

### 1462 **ALWAYS CHECK THAT YOU RECEIVE LAMICTAL**

1463 Patients prescribed LAMICTAL (lah-MICK-tall) have sometimes been given the wrong  
1464 medicine in error because many medicines have names similar to LAMICTAL. Taking the  
1465 wrong medication can cause serious health problems. When your healthcare provider gives you a  
1466 prescription for LAMICTAL

- 1467 • make sure you can read it clearly.
- 1468 • talk to your pharmacist to check that you are given the correct medicine.
- 1469 • check the tablets you receive against the pictures of the tablets below. The pictures show  
1470 actual tablet shape and size and the wording describes the color and printing that is on each  
1471 strength of LAMICTAL Tablets and Chewable Dispersible Tablets.

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### LAMICTAL (lamotrigine) Tablets

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

 <b>2 mg, white</b> <b>Imprinted with</b> <b>LTG 2</b>	 <b>5 mg, white</b> <b>Imprinted with</b> <b>GX CL2</b>	 <b>25 mg, white</b> <b>Imprinted with</b> <b>GX CL5</b>
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Please read this leaflet carefully before you take LAMICTAL and read the leaflet provided with any refill, in case any information has changed. This leaflet provides a summary of the information about your medicine. Please do not throw away this leaflet until you have finished your medicine. This leaflet does not contain all the information about LAMICTAL and is not meant to take the place of talking with your doctor. If you have any questions about LAMICTAL, ask your doctor or pharmacist.

#### 1489 **Information About Your Medicine:**

1490 The name of your medicine is LAMICTAL (lamotrigine). The decision to use LAMICTAL is  
1491 one that you and your doctor should make together. When taking lamotrigine, it is important to  
1492 follow your doctor's instructions.

#### 1493 1494 **1. The Purpose of Your Medicine:**

1495 **For Patients With Epilepsy:** LAMICTAL is intended to be used either alone or in  
1496 combination with other medicines to treat seizures in people aged 2 years or older.

1497 **For Patients With Bipolar Disorder:** LAMICTAL is used as maintenance treatment of  
1498 Bipolar I Disorder to delay the time to occurrence of mood episodes in people aged 18 years or  
1499 older treated for acute mood episodes with standard therapy.

1500 If you are taking LAMICTAL to help prevent extreme mood swings, you may not experience  
1501 the full effect for several weeks. Occasionally, the symptoms of depression or bipolar disorder  
1502 may include thoughts of harming yourself or committing suicide. Tell your doctor immediately  
1503 or go to the nearest hospital if you have any distressing thoughts or experiences during this initial

1504 period or at any other time. Also contact your doctor if you experience any worsening of your  
1505 condition or develop other new symptoms at any time during your treatment.

1506 Some medicines used to treat depression have been associated with suicidal thoughts and  
1507 suicidal behavior in children or teenagers. LAMICTAL is not approved for treating children or  
1508 teenagers with mood disorders such as bipolar disorder or depression.

1509 **2. Who Should Not Take LAMICTAL:**

1510 You should not take LAMICTAL if you had an allergic reaction to it in the past.

1511 **3. Side Effects to Watch for:**

- 1512 • Most people who take LAMICTAL tolerate it well. Common side effects with LAMICTAL  
1513 include dizziness, headache, blurred or double vision, lack of coordination, sleepiness,  
1514 nausea, vomiting, insomnia, and rash. LAMICTAL may cause other side effects not listed in  
1515 this leaflet. If you develop any side effects or symptoms you are concerned about or need  
1516 more information, call your doctor.
- 1517 • Although most patients who develop rash while receiving LAMICTAL have mild to  
1518 moderate symptoms, some individuals may develop a serious skin reaction that requires  
1519 hospitalization. Rarely, deaths have been reported. These serious skin reactions are most  
1520 likely to happen within the first 8 weeks of treatment with LAMICTAL. Serious skin  
1521 reactions occur more often in children than in adults.
- 1522 • Rashes may be more likely to occur if you: (1) take LAMICTAL in combination with  
1523 valproate [DEPAKENE<sup>®</sup> (valproic acid) or DEPAKOTE<sup>®</sup> (divalproex sodium)], (2) take a  
1524 higher starting dose of LAMICTAL than your doctor prescribed, or (3) increase your dose of  
1525 LAMICTAL faster than prescribed.
- 1526 • It is not possible to predict whether a mild rash will develop into a more serious reaction.  
1527 **Therefore, if you experience a skin rash, hives, fever, swollen lymph glands, painful**  
1528 **sores in the mouth or around the eyes, or swelling of lips or tongue, tell a doctor**  
1529 **immediately, since these symptoms may be the first signs of a serious reaction. A doctor**  
1530 **should evaluate your condition and decide if you should continue taking LAMICTAL.**

1531 **4. The Use of LAMICTAL During Pregnancy and Breast-feeding:**

1532 The effects of LAMICTAL during pregnancy are not known at this time. If you are pregnant  
1533 or are planning to become pregnant, talk to your doctor. Some LAMICTAL passes into breast  
1534 milk and the effects of this on infants are unknown. Therefore, if you are breast-feeding, you  
1535 should discuss this with your doctor to determine if you should continue to take LAMICTAL.

1536 **5. Use of Birth Control Pills or Other Female Hormonal Products:**

- 1537 • Do not start or stop using birth control pills or other female hormonal products until you have  
1538 consulted your doctor.
- 1539 • Tell your doctor as soon as possible if you experience changes in your menstrual pattern (e.g.,  
1540 break-through bleeding) while taking LAMICTAL and birth control pills or other female  
1541 hormonal products.

1542 **6. How to Use LAMICTAL:**

- 1543 • It is important to take LAMICTAL exactly as instructed by your doctor. The dose of  
1544 LAMICTAL must be increased slowly. It may take several weeks or months before your  
1545 final dosage can be determined by your doctor, based on your response.
- 1546 • Do not increase your dose of LAMICTAL or take more frequent doses than those indicated  
1547 by your doctor. Contact your doctor, if you stop taking LAMICTAL for any reason. Do not  
1548 restart without consulting your doctor.
- 1549 • If you miss a dose of LAMICTAL, do not double your next dose.
- 1550 • Always tell your doctor and pharmacist if you are taking any other prescription or  
1551 over-the-counter medicines. Tell your doctor before you start any other medicines.
- 1552 • Do NOT stop taking LAMICTAL or any of your other medicines unless instructed by your  
1553 doctor.
- 1554 • Use caution before driving a car or operating complex, hazardous machinery until you know  
1555 if LAMICTAL affects your ability to perform these tasks.
- 1556 • If you have epilepsy, tell your doctor if your seizures get worse or if you have any new types  
1557 of seizures.

1558 **7. How to Take LAMICTAL:**

1559 LAMICTAL Tablets should be swallowed whole. Chewing the tablets may leave a bitter taste.

1560 LAMICTAL Chewable Dispersible Tablets may be swallowed whole, chewed, or mixed in  
1561 water or diluted fruit juice. If the tablets are chewed, consume a small amount of water or diluted  
1562 fruit juice to aid in swallowing.

1563 To disperse LAMICTAL Chewable Dispersible Tablets, add the tablets to a small amount of  
1564 liquid (1 teaspoon, or enough to cover the medication) in a glass or spoon. Approximately  
1565 1 minute later, when the tablets are completely dispersed, mix the solution and take the entire  
1566 amount immediately.

1567 **8. Storing Your Medicine:**

1568 Store LAMICTAL at room temperature away from heat and light. Always keep your  
1569 medicines out of the reach of children.

1570 This medicine was prescribed for your use only to treat seizures or to treat Bipolar Disorder.  
1571 Do not give the drug to others.

1572 If your doctor decides to stop your treatment, do not keep any leftover medicine unless your  
1573 doctor tells you to. Throw away your medicine as instructed.

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GlaxoSmithKline

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1576 Manufactured for

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GlaxoSmithKline

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Research Triangle Park, NC 27709

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by DSM Pharmaceuticals, Inc.

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Greenville, NC 27834 or

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GlaxoSmithKline

1582 Research Triangle Park, NC 27709

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1588 August 2005

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

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**Information for the Patient**

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**LAMICTAL<sup>®</sup> (lamotrigine) Tablets**

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**LAMICTAL<sup>®</sup> (lamotrigine) Chewable Dispersible Tablets**

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1599 medicine in error because many medicines have names similar to LAMICTAL. Taking the  
1600 wrong medication can cause serious health problems. When your healthcare provider gives you a  
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- talk to your pharmacist to check that you are given the correct medicine.

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- check the tablets you receive against the pictures of the tablets below. The pictures show

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actual tablet shape and size and the wording describes the color and printing that is on each

1606

strength of LAMICTAL Tablets and Chewable Dispersible Tablets.

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1625

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1634 may include thoughts of harming yourself or committing suicide. Tell your doctor immediately

1635 or go to the nearest hospital if you have any distressing thoughts or experiences during this initial  
1636 period or at any other time. Also contact your doctor if you experience any worsening of your  
1637 condition or develop other new symptoms at any time during your treatment.

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1645 LAMICTAL include dizziness, headache, blurred or double vision, lack of coordination,  
1646 sleepiness, nausea, vomiting, insomnia, and rash. LAMICTAL may cause other side effects  
1647 not listed in this leaflet. If you develop any side effects or symptoms you are concerned about  
1648 or need more information, call your doctor.

1649 • Although most patients who develop rash while receiving LAMICTAL have mild to  
1650 moderate symptoms, some individuals may develop a serious skin reaction that requires  
1651 hospitalization. Rarely, deaths have been reported. These serious skin reactions are most  
1652 likely to happen within the first 8 weeks of treatment with LAMICTAL. Serious skin  
1653 reactions occur more often in children than in adults.

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1656 higher starting dose of LAMICTAL than your doctor prescribed, or (3) increase your dose of  
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1660 **sores in the mouth or around the eyes, or swelling of lips or tongue, tell a doctor**  
1661 **immediately, since these symptoms may be the first signs of a serious reaction. A doctor**  
1662 **should evaluate your condition and decide if you should continue taking LAMICTAL.**

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1665 or are planning to become pregnant, talk to your doctor. Some LAMICTAL passes into breast  
1666 milk and the effects of this on infants are unknown. Therefore, if you are breast-feeding, you  
1667 should discuss this with your doctor to determine if you should continue to take LAMICTAL.

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1669 • Do not start or stop using birth control pills or other female hormonal products until you have  
1670 consulted your doctor.

1671 • Tell your doctor as soon as possible if you experience changes in your menstrual pattern (e.g.,  
1672 break-through bleeding) while taking LAMICTAL and birth control pills or other female  
1673 hormonal products.

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1676 LAMICTAL must be increased slowly. It may take several weeks or months before your  
1677 final dosage can be determined by your doctor, based on your response.
- 1678 • Do not increase your dose of LAMICTAL or take more frequent doses than those indicated  
1679 by your doctor. Contact your doctor, if you stop taking LAMICTAL for any reason. Do not  
1680 restart without consulting your doctor.
- 1681 • If you miss a dose of LAMICTAL, do not double your next dose.
- 1682 • Always tell your doctor and pharmacist if you are taking any other prescription or  
1683 over-the-counter medicines. Tell your doctor before you start any other medicines.
- 1684 • Do NOT stop taking LAMICTAL or any of your other medicines unless instructed by your  
1685 doctor.
- 1686 • Use caution before driving a car or operating complex, hazardous machinery until you know  
1687 if LAMICTAL affects your ability to perform these tasks.
- 1688 • If you have epilepsy, tell your doctor if your seizures get worse or if you have any new types  
1689 of seizures.

1690 **7. How to Take LAMICTAL:**

1691 LAMICTAL Tablets should be swallowed whole. Chewing the tablets may leave a bitter taste.

1692 LAMICTAL Chewable Dispersible Tablets may be swallowed whole, chewed, or mixed in  
1693 water or diluted fruit juice. If the tablets are chewed, consume a small amount of water or diluted  
1694 fruit juice to aid in swallowing.

1695 To disperse LAMICTAL Chewable Dispersible Tablets, add the tablets to a small amount of  
1696 liquid (1 teaspoon, or enough to cover the medication) in a glass or spoon. Approximately  
1697 1 minute later, when the tablets are completely dispersed, mix the solution and take the entire  
1698 amount immediately.

1699 **8. Storing Your Medicine:**

1700 Store LAMICTAL at room temperature away from heat and light. Always keep your  
1701 medicines out of the reach of children.

1702 This medicine was prescribed for your use only to treat seizures or to treat Bipolar Disorder.  
1703 Do not give the drug to others.

1704 If your doctor decides to stop your treatment, do not keep any leftover medicine unless your  
1705 doctor tells you to. Throw away your medicine as instructed.

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GlaxoSmithKline

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Manufactured for

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GlaxoSmithKline

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Research Triangle Park, NC 27709

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by DSM Pharmaceuticals, Inc.

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Greenville, NC 27834 or

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GlaxoSmithKline

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