CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-764/S-011

20-241/S-017

APPROVED LABELING

PRESCRIBING INFORMATION

LAMICTAL®
(lamotrigine)
Tablets

LAMICTAL®
(lamotrigine)
Chewable Dispersible Tablets

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

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

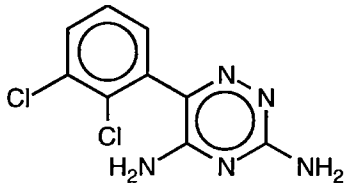
ESCALATION FOR LAMICTAL. HOWEVER, CASES HAVE BEEN REPORTED IN THE ABSENCE OF THESE FACTORS.

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

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

DESCRIPTION

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



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

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

starch glycolate.

CLINICAL PHARMACOLOGY

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

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

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

Pharmacological Properties: Although the relevance for human use is unknown, the following data characterize the performance of LAMICTAL in receptor binding assays. Lamotrigine had a weak inhibitory effect on the serotonin 5-HT_3 receptor (IC_{50} = 18 μM). It does not exhibit high affinity binding (IC_{50}>100 μM) to the following neurotransmitter receptors: adenosine A_1 and A_2; adrenergic α_1, α_2, and β; dopamine D_1 and D_2; γ-aminobutyric acid (GABA) A and B; histamine H_1; kappa opioid; muscarinic acetylcholine; and serotonin 5-HT_2. Studies have failed to detect an effect of lamotrigine on dihydropyridine-sensitive calcium channels. It had weak effects at sigma opioid receptors (IC_{50} = 145 μM). Lamotrigine did not inhibit the uptake of norepinephrine, dopamine, or serotonin (IC_{50}>200 μM) when tested in rat synaptosomes and/or human platelets in vitro.

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

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

partially returned to normal when supplemented with folinic acid.

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

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

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

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

132 **Table 1. Mean* Pharmacokinetic Parameters in Healthy Volunteers and Adult Patients**
133 **With Epilepsy**

Adult Study Population	Number of Subjects	T_{max}: Time of Maximum Plasma Concentration (h)	$t_{½}$: 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 enzyme-inducing antiepileptic drugs (EIAEDs)† 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 EIAEDs:				
Single-dose LAMICTAL	24	2.3 (0.5-5.0)	14.4 (6.4-30.4)	1.10 (0.51-2.22)
Multiple-dose LAMICTAL	17	2.0 (0.75-5.93)	12.6 (7.5-23.1)	1.21 (0.66-1.82)

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

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

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

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

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

Drug Interactions: **The apparent clearance of lamotrigine is affected by the coadministration of AEDs.** Lamotrigine is eliminated more rapidly in patients who have been taking hepatic EIAEDs, including carbamazepine, phenytoin, phenobarbital, and primidone. Most clinical experience is derived from this population.

Valproate decreases the apparent clearance of lamotrigine (i.e., more than doubles the elimination half-life of lamotrigine), whether given with or without EIAEDs. Accordingly, if lamotrigine is to be administered to a patient receiving valproate, lamotrigine must be given at a reduced dosage, no more than half the dose used in patients not receiving valproate (see

DOSAGE AND ADMINISTRATION and PRECAUTIONS: Drug Interactions).

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

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

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

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

Following multiple administrations (150 mg twice daily) to normal volunteers taking no other medications, lamotrigine induced its own metabolism, resulting in a 25% decrease in $t_{½}$ and a 37% increase in Cl/F at steady state compared to values obtained in the same volunteers following a single dose. Evidence gathered from other sources suggests that self-induction by LAMICTAL may not occur when LAMICTAL is given as adjunctive therapy in patients receiving EIAEDs.

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

Elimination: (see Table 1).

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

Hepatic Disease: The pharmacokinetics parameters of lamotrigine in patients with impaired liver function have not been studied.

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

212 therapy with other AEDS and 12 patients received LAMICTAL as monotherapy. Lamotrigine
213 pharmacokinetic parameters for pediatric patients are summarized in Table 2.
214 Population pharmacokinetic analyses involving patients aged 2 to 18 years demonstrated that
215 lamotrigine clearance was influenced predominantly by total body weight and concurrent AED
216 therapy. The oral clearance of lamotrigine was higher, on a body weight basis, in pediatric
217 patients than in adults. Weight-normalized lamotrigine clearance was higher in those subjects
218 weighing less than 30 kg, compared with those weighing greater than 30 kg. Accordingly,
219 patients weighing less than 30 kg may need an increase of as much as 50% in maintenance doses,
220 based on clinical response, as compared with subjects weighing more than 30 kg being
221 administered the same AEDs (see DOSAGE AND ADMINISTRATION). These analyses also
222 revealed that, after accounting for body weight, lamotrigine clearance was not significantly
223 influenced by age. Thus, the same weight-adjusted doses should be administered to children
224 irrespective of differences in age. Concomitant AEDs which influence lamotrigine clearance in
225 adults were found to have similar effects in children.
226

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

Pediatric Study Population	Number of Subjects	T_{max} (h)	$t_{½}$ (h)	Cl/F (mL/min/kg)
Ages 10 months-5.3 years				
Patients taking enzyme-inducing antiepileptic drugs (EIAEDs)	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 drug-metabolizing enzymes	7	5.2 (2.9-6.1)	19.0 (12.9-27.1)	1.2 (0.75-2.42)
Patients taking valproate only	8	2.9 (1.0-6.0)	44.9 (29.5-52.5)	0.47 (0.23-0.77)
Ages 5-11 years				
Patients taking EIAEDs	7	1.6 (1.0-3.0)	7.0 (3.8-9.8)	2.54 (1.35-5.58)
Patients taking EIAEDs plus valproate	8	3.3 (1.0-6.4)	19.1 (7.0-31.2)	0.89 (0.39-1.93)
Patients taking valproate only*	3	4.5 (3.0-6.0)	65.8 (50.7-73.7)	0.24 (0.21-0.26)
Ages 13-18 years				
Patients taking EIAEDs	11	†	†	1.3
Patients taking EIAEDs plus valproate	8	†	†	0.5
Patients taking valproate only	4	†	†	0.3

228 *Two subjects were included in the calculation for mean T_{max}.
229 † Parameter not estimated.
230
231 ***Elderly:*** The pharmacokinetics of lamotrigine following a single 150-mg dose of
232 LAMICTAL were evaluated in 12 elderly volunteers between the ages of 65 and 76 years (mean
233 creatinine clearance = 61 mL/min, range = 33 to 108 mL/min). The mean half-life of lamotrigine
234 in these subjects was 31.2 hours (range, 24.5 to 43.4 hours), and the mean clearance was
235 0.40 mL/min/kg (range, 0.26 to 0.48 mL/min/kg).
236 ***Gender:*** The clearance of lamotrigine is not affected by gender.
237 ***Race:*** The apparent oral clearance of lamotrigine was 25% lower in non-Caucasians than
238 Caucasians.
239
240 **CLINICAL STUDIES**

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

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

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

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

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

Adjunctive Therapy With LAMICTAL in Adults With Partial Seizures: The effectiveness of LAMICTAL as adjunctive therapy (added to other AEDs) was established in 3 multicenter, placebo-controlled, double-blind clinical trials in 355 adults with refractory partial seizures. The patients had a history of at least 4 partial seizures per month in spite of receiving one or more AEDs at therapeutic concentrations and, in 2 of the studies, were observed on their established AED regimen during baselines that varied between 8 to 12 weeks. In the third, patients were not observed in a prospective baseline. In patients continuing to have at least 4 seizures per month during the baseline, LAMICTAL or placebo was then added to the existing therapy. In all 3 studies, change from baseline in seizure frequency was the primary measure of effectiveness. The results given below are for all partial seizures in the intent-to-treat population

(all patients who received at least one dose of treatment) in each study, unless otherwise indicated. The median seizure frequency at baseline was 3 per week while the mean at baseline was 6.6 per week for all patients enrolled in efficacy studies.

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

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

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

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

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

Adjunctive Therapy With LAMICTAL in Pediatric and Adult Patients With

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

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

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

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

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

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

INDICATIONS AND USAGE

Epilepsy:

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

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

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

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

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

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

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

CONTRAINDICATIONS

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

WARNINGS

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

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

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

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

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

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

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

437 Other examples of serious and potentially life-threatening rash that did not lead to
438 hospitalization also occurred in premarketing development. Among these, 1 case was reported to
439 be Stevens-Johnson–like.
440 **Hypersensitivity Reactions:** Hypersensitivity reactions, some fatal or life threatening, have
441 also occurred. Some of these reactions have included clinical features of multiorgan
442 failure/dysfunction, including hepatic abnormalities and evidence of disseminated intravascular
443 coagulation. It is important to note that early manifestations of hypersensitivity (e.g., fever,
444 lymphadenopathy) may be present even though a rash is not evident. If such signs or symptoms
445 are present, the patient should be evaluated immediately. LAMICTAL should be discontinued if
446 an alternative etiology for the signs or symptoms cannot be established.
447 **Prior to initiation of treatment with LAMICTAL, the patient should be instructed that a**
448 **rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy) may**
449 **herald a serious medical event and that the patient should report any such occurrence to a**
450 **physician immediately.**
451 **Acute Multiorgan Failure:** Multiorgan failure, which in some cases has been fatal or
452 irreversible, has been observed in patients receiving LAMICTAL. Fatalities associated with
453 multiorgan failure and various degrees of hepatic failure have been reported in 2 of 3,796 adult
454 patients and 4 of 2,435 pediatric patients who received LAMICTAL in clinical trials. No such
455 fatalities have been reported in bipolar patients in clinical trials. Rare fatalities from multiorgan
456 failure have also been reported in compassionate plea and postmarketing use. The majority of
457 these deaths occurred in association with other serious medical events, including status
458 epilepticus and overwhelming sepsis, and hantavirus making it difficult to identify the initial
459 cause.
460 Additionally, 3 patients (a 45-year-old woman, a 3.5-year-old boy, and an 11-year-old girl)
461 developed multiorgan dysfunction and disseminated intravascular coagulation 9 to 14 days after
462 LAMICTAL was added to their AED regimens. Rash and elevated transaminases were also
463 present in all patients and rhabdomyolysis was noted in 2 patients. Both pediatric patients were
464 receiving concomitant therapy with valproate, while the adult patient was being treated with
465 carbamazepine and clonazepam. All patients subsequently recovered with supportive care after
466 treatment with LAMICTAL was discontinued.
467 **Blood Dyscrasias:** There have been reports of blood dyscrasias that may or may not be
468 associated with the hypersensitivity syndrome. These have included neutropenia, leukopenia,
469 anemia, thrombocytopenia, pancytopenia, and, rarely, aplastic anemia and pure red cell aplasia.
470 **Withdrawal Seizures:** As with other AEDs, LAMICTAL should not be abruptly discontinued.
471 In patients with epilepsy there is a possibility of increasing seizure frequency. In clinical trials in
472 patients with Bipolar Disorder, 2 patients experienced seizures shortly after abrupt withdrawal of
473 LAMICTAL. However, there were confounding factors that may have contributed to the
474 occurrence of seizures in these bipolar patients. Unless safety concerns require a more rapid
475 withdrawal, the dose of LAMICTAL should be tapered over a period of at least 2 weeks (see

DOSAGE AND ADMINISTRATION).

PRECAUTIONS

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

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

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

Use in Patients With Epilepsy:

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

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

515 similar population at about the same time. Importantly, that drug is chemically unrelated to
516 LAMICTAL. This evidence suggests, although it certainly does not prove, that the high SUDEP
517 rates reflect population rates, not a drug effect.
518 ***Status Epilepticus:*** Valid estimates of the incidence of treatment emergent status
519 epilepticus among patients treated with LAMICTAL are difficult to obtain because reporters
520 participating in clinical trials did not all employ identical rules for identifying cases. At a
521 minimum, 7 of 2,343 adult patients had episodes that could unequivocally be described as status.
522 In addition, a number of reports of variably defined episodes of seizure exacerbation (e.g.,
523 seizure clusters, seizure flurries, etc.) were made.
524 **Use in Patients With Bipolar Disorder:**
525 ***Acute Treatment of Mood Episodes*:** Safety and effectiveness of LAMICTAL in the
526 acute treatment of mood episodes has not been established.
527 ***Suicide*:** The possibility of a suicide attempt is inherent in Bipolar Disorder, and close
528 supervision of high-risk patients should accompany drug therapy. Prescriptions for LAMICTAL
529 should be written for the smallest quantity of tablets consistent with good patient management, in
530 order to reduce the risk of overdose. Overdoses have been reported for LAMICTAL, some of
531 which have been fatal (see OVERDOSAGE).
532 **Addition of LAMICTAL to a Multidrug Regimen That Includes Valproate (Dosage**
533 **Reduction):** Because valproate reduces the clearance of lamotrigine, the dosage of lamotrigine
534 in the presence of valproate is less than half of that required in its absence (see DOSAGE AND
535 ADMINISTRATION).
536 **Use in Patients With Concomitant Illness:** Clinical experience with LAMICTAL in
537 patients with concomitant illness is limited. Caution is advised when using LAMICTAL in
538 patients with diseases or conditions that could affect metabolism or elimination of the drug, such
539 as renal, hepatic, or cardiac functional impairment.
540 Hepatic metabolism to the glucuronide followed by renal excretion is the principal route of
541 elimination of lamotrigine (see CLINICAL PHARMACOLOGY).
542 A study in individuals with severe chronic renal failure (mean creatinine
543 clearance = 13 mL/min) not receiving other AEDs indicated that the elimination half-life of
544 unchanged lamotrigine is prolonged relative to individuals with normal renal function. Until
545 adequate numbers of patients with severe renal impairment have been evaluated during chronic
546 treatment with LAMICTAL, it should be used with caution in these patients, generally using a
547 reduced maintenance dose for patients with significant impairment.
548 Because there is no experience with the use of LAMICTAL in patients with impaired liver
549 function, the use in such patients may be associated with as yet unrecognized risks.
550 **Binding in the Eye and Other Melanin-Containing Tissues:** Because lamotrigine binds
551 to melanin, it could accumulate in melanin-rich tissues over time. This raises the possibility that
552 lamotrigine may cause toxicity in these tissues after extended use. Although ophthalmological
553 testing was performed in one controlled clinical trial, the testing was inadequate to exclude subtle

554 effects or injury occurring after long-term exposure. Moreover, the capacity of available tests to
555 detect potentially adverse consequences, if any, of lamotrigine's binding to melanin is unknown.
556 Accordingly, although there are no specific recommendations for periodic ophthalmological
557 monitoring, prescribers should be aware of the possibility of long-term ophthalmologic effects.
558 **Information for Patients:** Prior to initiation of treatment with LAMICTAL, the patient should
559 be instructed that a rash or other signs or symptoms of hypersensitivity (e.g., fever,
560 lymphadenopathy) may herald a serious medical event and that the patient should report any such
561 occurrence to a physician immediately. In addition, the patient should notify his or her physician
562 if worsening of seizure control occurs.
563 Patients should be advised that LAMICTAL may cause dizziness, somnolence, and other
564 symptoms and signs of central nervous system (CNS) depression. Accordingly, they should be
565 advised neither to drive a car nor to operate other complex machinery until they have gained
566 sufficient experience on LAMICTAL to gauge whether or not it adversely affects their mental
567 and/or motor performance.
568 Patients should be advised to notify their physicians if they become pregnant or intend to
569 become pregnant during therapy. Patients should be advised to notify their physicians if they
570 intend to breast-feed or are breast-feeding an infant.
571 Patients should be informed of the availability of a patient information leaflet, and they should
572 be instructed to read the leaflet prior to taking LAMICTAL. See PATIENT INFORMATION at
573 the end of this labeling for the text of the leaflet provided for patients.
574 **Laboratory Tests:** The value of monitoring plasma concentrations of LAMICTAL has not
575 been established. Because of the possible pharmacokinetic interactions between LAMICTAL and
576 other AEDs being taken concomitantly (see Table 3), monitoring of the plasma levels of
577 LAMICTAL and concomitant AEDs may be indicated, particularly during dosage adjustments. In
578 general, clinical judgment should be exercised regarding monitoring of plasma levels of
579 LAMICTAL and other anti-seizure drugs and whether or not dosage adjustments are necessary.
580 **Drug Interactions:**
581 ***Effects of Lamotrigine on the Pharmacokinetics of Other Drugs:*** (see Table 3).
582 ***LAMICTAL Added to Carbamazepine:*** LAMICTAL has no appreciable effect on
583 steady-state carbamazepine plasma concentration. Limited clinical data suggest there is a higher
584 incidence of dizziness, diplopia, ataxia, and blurred vision in patients receiving carbamazepine
585 with LAMICTAL than in patients receiving other EIAEDs with LAMICTAL (see ADVERSE
586 REACTIONS). The mechanism of this interaction is unclear. The effect of lamotrigine on plasma
587 concentrations of carbamazepine-epoxide is unclear. In a small subset of patients (n = 7) studied
588 in a placebo-controlled trial, lamotrigine had no effect on carbamazepine-epoxide plasma
589 concentrations, but in a small, uncontrolled study (n = 9), carbamazepine-epoxide levels were
590 seen to increase.
591 ***LAMICTAL Added to Valproate:*** When LAMICTAL was administered to 18 healthy
592 volunteers receiving valproate in a pharmacokinetic study, the trough steady-state valproate

concentrations in plasma decreased by an average of 25% over a 3-week period, and then stabilized. However, adding LAMICTAL to the existing therapy did not cause a change in plasma valproate concentrations in either adult or pediatric patients in controlled clinical trials.

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

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

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

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

Valproate Added to LAMICTAL: The addition of valproate increases lamotrigine steady-state concentrations in normal volunteers by slightly more than 2-fold.

Enzyme-Inducing Antiepileptic Drugs (e.g., carbamazepine, phenytoin, phenobarbital, primidone) Added to LAMICTAL: The addition of EIAEDs decreases lamotrigine steady-state concentrations by approximately 40%.

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

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

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

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

Table 3. Summary of Drug Interactions With LAMICTAL

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

*From adjunctive clinical trials and volunteer studies.
†Net effects were estimated by comparing the mean clearance values obtained in adjunctive clinical trials and volunteers studies.
‡Not administered, but an active metabolite of carbamazepine.
↔ = No significant effect.
? = Conflicting data.

Drug/Laboratory Test Interactions: None known.

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

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

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

Pregnancy: Pregnancy Category C. No evidence of teratogenicity was found in mice, rats, or rabbits when lamotrigine was orally administered to pregnant animals during the period of organogenesis at doses up to 1.2, 0.5, and 1.1 times, respectively, on a mg/m^2 basis, the highest

usual human maintenance dose (i.e., 500 mg/day). However, maternal toxicity and secondary fetal toxicity producing reduced fetal weight and/or delayed ossification were seen in mice and rats, but not in rabbits at these doses. Teratology studies were also conducted using bolus intravenous administration of the isethionate salt of lamotrigine in rats and rabbits. In rat dams administered an intravenous dose at 0.6 times the highest usual human maintenance dose, the incidence of intrauterine death without signs of teratogenicity was increased.

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

Epilepsy:

Most Common Adverse Events in All Clinical Studies: Adjunctive Therapy in Adults With Epilepsy: The most commonly observed (≥5%) adverse experiences seen in association with LAMICTAL during adjunctive therapy in adults and not seen at an equivalent frequency among placebo-treated patients were: dizziness, ataxia, somnolence, headache, diplopia, blurred vision, nausea, vomiting, and rash. Dizziness, diplopia, ataxia, blurred vision, nausea, and vomiting were dose related. Dizziness, diplopia, ataxia, and blurred vision occurred more commonly in patients receiving carbamazepine with LAMICTAL than in patients receiving other EIAEDs with LAMICTAL. Clinical data suggest a higher incidence of rash, including serious rash, in patients receiving concomitant valproate than in patients not receiving valproate (see WARNINGS).

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

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

Monotherapy in Adults With Epilepsy: The most commonly observed (≥5%) adverse experiences seen in association with the use of LAMICTAL during the monotherapy phase of the controlled trial in adults not seen at an equivalent rate in the control group were vomiting,

727 coordination abnormality, dyspepsia, nausea, dizziness, rhinitis, anxiety, insomnia, infection,
728 pain, weight decrease, chest pain, and dysmenorrhea. The most commonly observed (≥5%)
729 adverse experiences associated with the use of LAMICTAL during the conversion to
730 monotherapy (add-on) period, not seen at an equivalent frequency among low-dose
731 valproate-treated patients, were dizziness, headache, nausea, asthenia, coordination abnormality,
732 vomiting, rash, somnolence, diplopia, ataxia, accidental injury, tremor, blurred vision, insomnia,
733 nystagmus, diarrhea, lymphadenopathy, pruritus, and sinusitis.
734 Approximately 10% of the 420 adult patients who received LAMICTAL as monotherapy in
735 premarketing clinical trials discontinued treatment because of an adverse experience. The adverse
736 events most commonly associated with discontinuation were rash (4.5%), headache (3.1%), and
737 asthenia (2.4%).
738 ***Adjunctive Therapy in Pediatric Patients With Epilepsy:*** The most commonly
739 observed (≥5%) adverse experiences seen in association with the use of LAMICTAL as
740 adjunctive treatment in pediatric patients and not seen at an equivalent rate in the control group
741 were infection, vomiting, rash, fever, somnolence, accidental injury, dizziness, diarrhea,
742 abdominal pain, nausea, ataxia, tremor, asthenia, bronchitis, flu syndrome, and diplopia.
743 In 339 patients age 2 to 16 years, 4.2% of patients on LAMICTAL and 2.9% of patients on
744 placebo discontinued due to adverse experiences. The most commonly reported adverse
745 experiences that led to discontinuation were rash for patients treated with LAMICTAL and
746 deterioration of seizure control for patients treated with placebo.
747 Approximately 11.5% of the 1,081 pediatric patients who received LAMICTAL as adjunctive
748 therapy in premarketing clinical trials discontinued treatment because of an adverse experience.
749 The adverse events most commonly associated with discontinuation were rash (4.4%), reaction
750 aggravated (1.7%), and ataxia (0.6%).
751 ***Incidence in Controlled Clinical Studies of Epilepsy:*** The prescriber should be aware
752 that the figures in Tables 4, 5, 6, and 7 cannot be used to predict the frequency of adverse
753 experiences in the course of usual medical practice where patient characteristics and other factors
754 may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot
755 be directly compared with figures obtained from other clinical investigations involving different
756 treatments, uses, or investigators. An inspection of these frequencies, however, does provide the
757 prescriber with one basis to estimate the relative contribution of drug and nondrug factors to the
758 adverse event incidences in the population studied.
759 ***Incidence in Controlled Adjunctive Clinical Studies in Adults With Epilepsy:***
760 Table 4 lists treatment-emergent signs and symptoms that occurred in at least 2% of adult
761 patients with epilepsy treated with LAMICTAL in placebo-controlled trials and were numerically
762 more common in the patients treated with LAMICTAL. In these studies, either LAMICTAL or
763 placebo was added to the patient's current AED therapy. Adverse events were usually mild to
764 moderate in intensity.

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

Body System/ Adverse Experience†	Percent of Patients Receiving Adjunctive LAMICTAL (n = 711)	Percent of Patients Receiving Adjunctive Placebo (n = 419)
Body as a whole		
Headache	29	19
Flu syndrome	7	6
Fever	6	4
Abdominal pain	5	4
Neck pain	2	1
Reaction aggravated (seizure exacerbation)	2	1
Digestive		
Nausea	19	10
Vomiting	9	4
Diarrhea	6	4
Dyspepsia	5	2
Constipation	4	3
Tooth disorder	3	2
Anorexia	2	1
Musculoskeletal		
Arthralgia	2	0
Nervous		
Dizziness	38	13
Ataxia	22	6
Somnolence	14	7
Incoordination	6	2
Insomnia	6	2
Tremor	4	1
Depression	4	3
Anxiety	4	3
Convulsion	3	1
Irritability	3	2
Speech disorder	3	0

Concentration disturbance	2	1
Respiratory		
Rhinitis	14	9
Pharyngitis	10	9
Cough increased	8	6
Skin and appendages		
Rash	10	5
Pruritus	3	2
Special senses		
Diplopia	28	7
Blurred vision	16	5
Vision abnormality	3	1
Urogenital		
Female patients only	(n = 365)	(n = 207)
Dysmenorrhea	7	6
Vaginitis	4	1
Amenorrhea	2	1

* Patients in these adjunctive studies were receiving 1 to 3 concomitant EIAEDs in addition to LAMICTAL or placebo. Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category.
† Adverse experiences reported by at least 2% of patients treated with LAMICTAL are included.

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

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

	Percent of Patients Experiencing Adverse Experiences		
Adverse Experience	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*

*Significantly greater than placebo group ($p<0.05$).
†Significantly greater than group receiving LAMICTAL 300 mg ($p<0.05$).

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

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

Incidence in a Controlled Monotherapy Trial in Adults With Partial Seizures: Table 6 lists treatment-emergent signs and symptoms that occurred in at least 5% of patients with epilepsy treated with monotherapy with LAMICTAL in a double-blind trial following discontinuation of either concomitant carbamazepine or phenytoin not seen at an equivalent frequency in the control group.

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

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

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

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

‡ Up to 500 mg/day.

§ 1,000 mg/day.

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

Body as a Whole: Asthenia, fever.

Digestive: Anorexia, dry mouth, rectal hemorrhage, peptic ulcer.

Metabolic and Nutritional: Peripheral edema.

Nervous System: Amnesia, ataxia, depression, hypesthesia, libido increase, decreased reflexes, increased reflexes, nystagmus, irritability, suicidal ideation.

Respiratory: Epistaxis, bronchitis, dyspnea.

Skin and Appendages: Contact dermatitis, dry skin, sweating.

Special Senses: Vision abnormality.

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

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

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

Ataxia	11	3
Tremor	10	1
Emotional lability	4	2
Gait abnormality	4	2
Thinking abnormality	3	2
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
Vision abnormality	2	0
Urogenital		
Male and female patients		
Urinary tract infection	3	0
Male patients only	n = 93	n = 92
Penis disorder	2	0

Bipolar Disorder: The most commonly observed (≥5%) adverse experiences seen in association with the use of LAMICTAL as monotherapy (100 to 400 mg/day) in Bipolar Disorder in the 2 double-blind, placebo-controlled trials of 18 months' duration, and numerically more

834 frequent than in placebo-treated patients are included in Table 8. Adverse events that occurred in
835 at least 5% of patients and were numerically more common during the dose escalation phase of
836 LAMICTAL in these trials (when patients may have been receiving concomitant medications)
837 compared to the monotherapy phase were: headache (25%), rash (11%), dizziness (10%),
838 diarrhea (8%), dream abnormality (6%), and pruritus (6%).
839 During the monotherapy phase of the double-blind, placebo-controlled trials of 18 months'
840 duration, 13% of 227 patients who received LAMICTAL (100 to 400 mg/day), 16% of
841 190 patients who received placebo, and 23% of 166 patients who received lithium discontinued
842 therapy because of an adverse experience. The adverse events which most commonly led to
843 discontinuation of LAMICTAL were rash (3%) and mania/hypomania/mixed mood adverse
844 events (2%). Approximately 16% of 2,401 patients who received LAMICTAL (50 to
845 500 mg/day) for Bipolar Disorder in premarketing trials discontinued therapy because of an
846 adverse experience; most commonly due to rash (5%) and mania/hypomania/mixed mood
847 adverse events (2%).
848 ***Incidence in Controlled Clinical Studies of LAMICTAL for the Maintenance***
849 ***Treatment of Bipolar I Disorder:*** Table 8 lists treatment-emergent signs and symptoms that
850 occurred in at least 5% of patients with Bipolar Disorder treated with LAMICTAL monotherapy
851 (100 to 400 mg/day), following the discontinuation of other psychotropic drugs, in 2
852 double-blind, placebo-controlled trials of 18 months' duration and were numerically more
853 frequent than in the placebo group.
854

855 **Table 8. Treatment-Emergent Adverse Event Incidence in 2 Placebo-Controlled Trials**
856 **in Adults With Bipolar I Disorder* (Events in at least 5% of patients treated with**
857 **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 (non serious)‡	7	5

858 * Patients in these studies were converted to LAMICTAL (100 to 400 mg/day) or placebo
859 monotherapy from add-on therapy with other psychotropic medications. Patients may
860 have reported multiple adverse experiences during the study; thus, patients may be
861 included in more than one category.
862 † Adverse experiences reported by at least 5% of patients are included.
863 ‡ In the overall bipolar and other mood disorders clinical trials, the rate of serious rash was
864 0.08% (1 of 1,233) of adult patients who received LAMICTAL as initial monotherapy
865 and 0.13% (2 of 1,538) of adult patients who received LAMICTAL as adjunctive therapy
866 (see WARNINGS).
867
868 These adverse events were usually mild to moderate in intensity.
869 Other events that occurred in 5% or more patients but equally or more frequently in the
870 placebo group included: dizziness, mania, headache, infection, influenza, pain, accidental injury,
871 diarrhea, and dyspepsia.

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

General: Fever, neck pain.

Cardiovascular: Migraine.

Digestive: Flatulence.

Metabolic and Nutritional: Weight gain, edema.

Musculoskeletal: Arthralgia, myalgia.

Nervous System: Amnesia, depression, agitation, emotional lability, dyspraxia, abnormal thoughts, dream abnormality, hypoesthesia.

Respiratory: Sinusitis.

Urogenital: Urinary frequency.

Adverse Events Following Abrupt Discontinuation: In the 2 maintenance trials, there was no increase in the incidence, severity or type of adverse events in Bipolar Disorder patients after abruptly terminating LAMICTAL therapy. In clinical trials in patients with Bipolar Disorder, 2 patients experienced seizures shortly after abrupt withdrawal of LAMICTAL. However, there were confounding factors that may have contributed to the occurrence of seizures in these bipolar patients (see DOSAGE AND ADMINISTRATION).

Mania/Hypomania/Mixed Episodes: During the double-blind, placebo-controlled clinical trials in Bipolar I Disorder in which patients were converted to LAMICTAL monotherapy (100 to 400 mg/day) from other psychotropic medications and followed for durations up to 18 months, the rate of manic or hypomanic or mixed mood episodes reported as adverse experiences was 5% for patients treated with LAMICTAL (n = 227), 4% for patients treated with lithium (n = 166), and 7% for patient treated with placebo (n = 190). In all bipolar controlled trials combined, adverse events of mania (including hypomania and mixed mood episodes) were reported in 5% of patients treated with LAMICTAL (n = 956), 3% of patients treated with lithium (n = 280), and 4% of patients treated with placebo (n = 803).

The overall adverse event profile for LAMICTAL was similar between females and males, between elderly and nonelderly patients, and among racial groups.

Other Adverse Events Observed During All Clinical Trials For Pediatric and Adult Patients With Epilepsy or Bipolar Disorder and Other Mood Disorders: LAMICTAL has been administered to 6,694 individuals for whom complete adverse event data was captured during all clinical trials, only some of which were placebo controlled. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. The frequencies presented represent the proportion of the 6,694 individuals exposed to LAMICTAL who experienced an event of the type cited on at least one occasion while receiving LAMICTAL. All reported events are included except those already listed in the previous tables or elsewhere in the labeling, those too general to be informative, and those not reasonably associated with the use of the drug.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* adverse events are defined as those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1,000 patients; *rare* adverse events are those occurring in fewer than 1/1,000 patients.

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

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

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

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

Endocrine System: Rare: Goiter and hypothyroidism.

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

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

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

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

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

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

defect.

Urogenital System: Infrequent: Abnormal ejaculation, breast pain, hematuria, impotence, menorrhagia, polyuria, urinary incontinence, and urine abnormality. ***Rare:*** Acute kidney failure, anorgasmia, breast abscess, breast neoplasm, creatinine increase, cystitis, dysuria, epididymitis, female lactation, kidney failure, kidney pain, nocturia, urinary retention, urinary urgency, and vaginal moniliasis.

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

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

Gastrointestinal: Esophagitis.

Hepatobiliary Tract and Pancreas: Pancreatitis.

Immunologic: Lupus-like reaction, vasculitis.

Lower Respiratory: Apnea.

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

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

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

DRUG ABUSE AND DEPENDENCE

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

OVERDOSAGE

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

Management of Overdose: There are no specific antidotes for LAMICTAL. Following a suspected overdose, hospitalization of the patient is advised. General supportive care is indicated, including frequent monitoring of vital signs and close observation of the patient. If indicated, emesis should be induced or gastric lavage should be performed; usual precautions should be taken to protect the airway. It should be kept in mind that lamotrigine is rapidly absorbed (see CLINICAL PHARMACOLOGY). It is uncertain whether hemodialysis is an effective means of

removing lamotrigine from the blood. In 6 renal failure patients, about 20% of the amount of lamotrigine in the body was removed by hemodialysis during a 4-hour session. A Poison Control Center should be contacted for information on the management of overdosage of LAMICTAL.

DOSAGE AND ADMINISTRATION

Epilepsy:

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

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

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

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

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

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

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

Epilepsy:

1029 ***Adjunctive Therapy With LAMICTAL for Epilepsy:*** This section provides specific
1030 dosing recommendations for patients 2 to 12 years of age and patients greater than 12 years of
1031 age. Within each of these age-groups, specific dosing recommendations are provided depending
1032 upon whether or not the patient is receiving valproate (Tables 9 and 10 for patients 2 to 12 years
1033 of age, Tables 11 and 12 for patients greater than 12 years of age). In addition, the section
1034 provides a discussion of dosing for those patients receiving concomitant AEDs that have not
1035 been systematically evaluated in combination with LAMICTAL.
1036 For dosing guidelines for LAMICTAL below, enzyme-inducing antiepileptic drugs (EIAEDs)
1037 include phenytoin, carbamazepine, phenobarbital, and primidone.
1038 ***Patients 2 to 12 Years of Age:*** Recommended dosing guidelines for LAMICTAL
1039 added to an antiepileptic drug (AED) regimen containing valproate are summarized in Table 9.
1040 Recommended dosing guidelines for LAMICTAL added to EIAEDs are summarized in Table 10.
1041 ***LAMICTAL Added to Antiepileptic Drugs Other Than Enzyme-Inducing***
1042 ***Antiepileptic Drugs and Valproate:*** The effect of AEDs other than EIAEDs and valproate
1043 on the metabolism of LAMICTAL is not currently known. Therefore, no specific dosing
1044 guidelines can be provided in that situation. Conservative starting doses and dose escalations (as
1045 with concomitant valproate) would be prudent; maintenance dosing would be expected to fall
1046 between the maintenance dose with valproate and the maintenance dose without valproate, but
1047 with an EIAED.
1048 Note that the starting doses and dose escalations listed in Tables 9 and 10 are different than
1049 those used in clinical trials; however, the maintenance doses are the same as in clinical trials.
1050 Smaller starting doses and slower dose escalations than those used in clinical trials are
1051 recommended because of the suggestions that the risk of rash may be decreased by smaller
1052 starting doses and slower dose escalations. Therefore, maintenance doses will take longer to
1053 reach in clinical practice than in clinical trials. It may take several weeks to months to achieve an
1054 individualized maintenance dose. Maintenance doses in patients weighing less than 30 kg,
1055 regardless of age or concomitant AED, may need to be increased as much as 50%, based on
1056 clinical response.
1057 **The smallest available strength of LAMICTAL Chewable Dispersible Tablets is 2 mg,**
1058 **and only whole tablets should be administered. If the calculated dose cannot be achieved**
1059 **using whole tablets, the dose should be rounded down to the nearest whole tablet (see**
1060 **HOW SUPPLIED and PATIENT INFORMATION for a description of the available sizes**
1061 **of LAMICTAL Chewable Dispersible Tablets).**
1062

1063 **Table 9. LAMICTAL Added to an Antiepileptic Regimen Containing Valproate in**
1064 **Patients 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 *other* day	2 mg every day
14.1 kg	27 kg	2 mg every day	4 mg every day
27.1 kg	34 kg	4 mg every day	8 mg every day
34.1 kg	40 kg	5 mg every day	10 mg every day
Usual maintenance dose: 1 to 5 mg/kg/day (maximum 200 mg/day in 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.			

1065

1066 **Table 10. LAMICTAL Added to Enzyme-Inducing Antiepileptic Drugs (Without**
1067 **Valproate) in Patients 2 to 12 Years of Age**

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.
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.	

1068

1069 ***Patients Over 12 Years of Age:*** Recommended dosing guidelines for LAMICTAL
1070 added to valproate are summarized in Table 11. Recommended dosing guidelines for

LAMICTAL added to EIAEDs are summarized in Table 12.

LAMICTAL Added to Antiepileptic Drugs Other Than Enzyme-Inducing Antiepileptic Drugs and Valproate: The effect of AEDs other than EIAEDs and valproate on the metabolism of LAMICTAL is not currently known. Therefore, no specific dosing guidelines can be provided in that situation. Conservative starting doses and dose escalations (as with concomitant valproate) would be prudent; maintenance dosing would be expected to fall between the maintenance dose with valproate and the maintenance dose without valproate, but with an EIAED.

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

Weeks 1 and 2	25 mg every *other* 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.	

Table 12. LAMICTAL Added to Enzyme-Inducing Antiepileptic Drugs (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.	

Conversion From a Single Enzyme-Inducing Antiepileptic Drug to Monotherapy With LAMICTAL in Patients ≥16 Years of Age With Epilepsy: The goal of the transition regimen is to effect the conversion to monotherapy with LAMICTAL under conditions that ensure adequate seizure control while mitigating the risk of serious rash associated with the rapid titration of LAMICTAL.

The conversion regimen involves 2 steps. In the first, LAMICTAL is titrated to the targeted dose while maintaining the dose of the EIAED at a fixed level; in the second step, the EIAED is gradually withdrawn over a period of 4 weeks.

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

LAMICTAL should be added to an EIAED to achieve a dose of 500 mg/day according to the guidelines in Table 12 above. The regimen for the withdrawal of the concomitant EIAED is

1098 based on experience gained in the controlled monotherapy clinical trial. In that trial, the
1099 concomitant EIAED was withdrawn by 20% decrements each week over a 4-week period.
1100 Because of an increased risk of rash, the recommended initial dose and subsequent dose
1101 escalations of LAMICTAL should not be exceeded (see BOX WARNING).
1102 ***Conversion from the Combination of LAMICTAL and Valproate to Monotherapy***
1103 ***With LAMICTAL in Patients ≥ 16 Years of Age With Epilepsy:*** Discontinuing valproate
1104 is known to shorten the half-life of lamotrigine. However, there is insufficient information to
1105 provide dosing guidelines for this conversion. The safety and effectiveness of LAMICTAL has
1106 not been established for the conversion to monotherapy from the 2 drug combination of
1107 LAMICTAL and valproate in patients with epilepsy.
1108 ***Usual Maintenance Dose for Epilepsy:*** The usual maintenance doses identified in the
1109 tables above are derived from dosing regimens employed in the placebo-controlled adjunctive
1110 studies in which the efficacy of LAMICTAL was established. In patients receiving multidrug
1111 regimens employing EIAEDs **without valproate**, maintenance doses of adjunctive LAMICTAL
1112 as high as 700 mg/day have been used. In patients receiving **valproate alone**, maintenance doses
1113 of adjunctive LAMICTAL as high as 200 mg/day have been used. The advantage of using doses
1114 above those recommended in the tables above has not been established in controlled trials.
1115 ***Discontinuation Strategy for Patients With Epilepsy:*** For patients receiving
1116 LAMICTAL in combination with other AEDs, a reevaluation of all AEDs in the regimen should
1117 be considered if a change in seizure control or an appearance or worsening of adverse
1118 experiences is observed.
1119 If a decision is made to discontinue therapy with LAMICTAL, a step-wise reduction of dose
1120 over at least 2 weeks (approximately 50% per week) is recommended unless safety concerns
1121 require a more rapid withdrawal (see PRECAUTIONS).
1122 *Discontinuing an EIAED should prolong the half-life of lamotrigine; discontinuing valproate*
1123 *should shorten the half-life of lamotrigine.*
1124 ***Target Plasma Levels for Patients With Epilepsy:*** A therapeutic plasma concentration
1125 range has not been established for lamotrigine. Dosing of LAMICTAL should be based on
1126 therapeutic response.
1127 **Bipolar Disorder:** The goal of maintenance treatment with LAMICTAL is to delay the time to
1128 occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated
1129 for acute mood episodes with standard therapy. The target dose of LAMICTAL is 200 mg/day
1130 (100 mg/day in combination with valproate and 400 mg/day in combination with carbamazepine
1131 or other enzyme-inducing drugs). In the clinical trials, doses up to 400 mg/day as monotherapy
1132 were evaluated, however, no additional benefit was seen at 400 mg/day compared to 200 mg/day
1133 (see CLINICAL STUDIES: Bipolar Disorder). Accordingly, doses above 200 mg/day are not
1134 recommended. Treatment with LAMICTAL is introduced, based on concurrent medications,
1135 according to the regimen outlined in Table 13. If other psychotropic medications are withdrawn
1136 following stabilization, the dose of LAMICTAL should be adjusted. For patients discontinuing
1137 valproate, the dose of LAMICTAL should be doubled over a 2 week period in equal weekly

increments (see Table 14). For patients discontinuing carbamazepine or other enzyme inducing agents, the dose of LAMICTAL should remain constant for the first week and then should be decreased by half over a 2 week period in equal weekly decrements (see Table 14). The dose of LAMICTAL may then be further adjusted to the target dose (200 mg) as clinically indicated.

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

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

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

	For Patients Not Taking Carbamazepine (or Other Enzyme-Inducing Drugs) or Valproate	For Patients Taking Valproate	For Patients Taking Carbamazepine (or Other Enzyme-Inducing Drugs) and Not Taking Valproate
Weeks 1 and 2	25 mg daily	25 mg every other day	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

1150 **Table 14. Adjustments to LAMICTAL Dosing for Patients With Bipolar Disorder**
1151 **Following Discontinuation of Psychotropic Medications**

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

1152
1153 There is no body of evidence available to answer the question of how long the patient should
1154 remain on LAMICTAL therapy. Systematic evaluation of the efficacy of LAMICTAL in patients
1155 with either depression or mania who responded to standard therapy during an acute 8 to 16 week
1156 treatment phase and were then randomized to LAMICTAL or placebo for up to 76 weeks of
1157 observation for affective relapse demonstrated a benefit of such maintenance treatment (see
1158 CLINICAL STUDIES: Bipolar Disorder). Nevertheless, patients should be periodically
1159 reassessed to determine the need for maintenance treatment.
1160 ***Discontinuation Strategy in Bipolar Disorder:*** As with other AEDs, LAMICTAL
1161 should not be abruptly discontinued. In the controlled clinical trials, there was no increase in the
1162 incidence, type, or severity of adverse experiences following abrupt termination of LAMICTAL.
1163 In clinical trials in patients with bipolar disorder, 2 patients experienced seizures shortly after
1164 abrupt withdrawal of LAMICTAL. However, there were confounding factors that may have
1165 contributed to the occurrence of seizures in these bipolar patients. Discontinuation of
1166 LAMICTAL should involve a step-wise reduction of dose over at least 2 weeks (approximately
1167 50% per week) unless safety concerns require a more rapid withdrawal.
1168 **Administration of LAMICTAL Chewable Dispersible Tablets:** LAMICTAL Chewable
1169 Dispersible Tablets may be swallowed whole, chewed, or dispersed in water or diluted fruit juice.
1170 If the tablets are chewed, consume a small amount of water or diluted fruit juice to aid in
1171 swallowing.
1172 To disperse LAMICTAL Chewable Dispersible Tablets, add the tablets to a small amount of
1173 liquid (1 teaspoon, or enough to cover the medication). Approximately 1 minute later, when the
1174 tablets are completely dispersed, swirl the solution and consume the entire quantity immediately.
1175 *No attempt should be made to administer partial quantities of the dispersed tablets.*

HOW SUPPLIED

LAMICTAL Tablets, 25-mg

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

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

LAMICTAL Tablets, 100-mg

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

LAMICTAL Tablets, 150-mg

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

LAMICTAL Tablets, 200-mg

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

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

LAMICTAL Chewable Dispersible Tablets, 2-mg

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

LAMICTAL Chewable Dispersible Tablets, 5-mg

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

LAMICTAL Chewable Dispersible Tablets, 25-mg

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

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

LAMICTAL Starter Kit for Patients Taking Valproate

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

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

LAMICTAL Starter Kit for Patients Taking Enzyme-Inducing Drugs and Not Taking Valproate

25-mg, white, scored, shield-shaped tablets debossed with "LAMICTAL" and "25" and **100-mg**, peach, scored, shield-shaped tablets debossed with "LAMICTAL" and "100", blisterpack of 84, 25-mg tablets and 14, 100-mg tablets (NDC 0081-0594-01).

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

LAMICTAL Starter Kit for Patients Not Taking Enzyme-Inducing Drugs or Valproate [FOR USE IN BIPOLAR PATIENTS ONLY]

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

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

PATIENT INFORMATION

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

Information for the Patient

LAMICTAL® (lamotrigine) Tablets

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

LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

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

NOTE: The pictures above show actual tablet shape and size and the wording describes the color and printing that is on each strength of LAMICTAL Tablets and Chewable

Dispersible Tablets. Before taking your medicine, it is important to compare the tablets you receive from your doctor or pharmacist with these pictures to make sure you have received the correct medicine.

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

Information About Your Medicine:

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

1. The Purpose of Your Medicine:

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

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

2. Who Should Not Take LAMICTAL:

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

3. Side Effects to Watch for:

- Most people who take LAMICTAL tolerate it well. Common side effects with LAMICTAL include dizziness, headache, blurred or double vision, lack of coordination, sleepiness, nausea, vomiting, insomnia, and rash. LAMICTAL may cause other side effects not listed in this leaflet. If you develop any side effects or symptoms you are concerned about or need more information, call your doctor.
- Although most patients who develop rash while receiving LAMICTAL have mild to moderate symptoms, some individuals may develop a serious skin reaction that requires hospitalization. Rarely, deaths have been reported. These serious skin reactions are most likely to happen within the first 8 weeks of treatment with LAMICTAL. Serious skin reactions occur more often in children than in adults.
- Rashes may be more likely to occur if you: (1) take LAMICTAL in combination with valproate [DEPAKENE® (valproic acid) or DEPAKOTE® (divalproex sodium)], (2) take a higher starting dose of LAMICTAL than your doctor prescribed, or (3) increase your dose of LAMICTAL faster than prescribed.
- It is not possible to predict whether a mild rash will develop into a more serious reaction.

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

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

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

5. How to Use LAMICTAL:

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

6. How to Take LAMICTAL:

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

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

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

7. Storing Your Medicine:

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

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

If your doctor decides to stop your treatment, do not keep any leftover medicine unless your

doctor tells you to. Throw away your medicine as instructed.

GlaxoSmithKline
Research Triangle Park, NC 27709

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PHARMACIST--DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

Information for the Patient

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LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

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

NOTE: The pictures above show actual tablet shape and size and the wording describes the color and printing that is on each strength of LAMICTAL Tablets and Chewable

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- If you miss a dose of LAMICTAL, do not double your next dose.
- Do NOT stop taking LAMICTAL or any of your other medicines unless instructed by your doctor.
- Use caution before driving a car or operating complex, hazardous machinery until you know if LAMICTAL affects your ability to perform these tasks.
- If you have epilepsy, tell your doctor if your seizures get worse or if you have any new types of seizures.
- Always tell your doctor and pharmacist if you are taking or plan to take any other prescription or over-the-counter medicines.

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