**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.**

**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.**

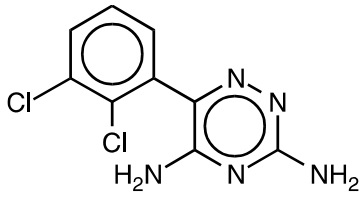
**NEARLY ALL CASES OF LIFE-THREATENING RASHES ASSOCIATED WITH LAMICTAL HAVE OCCURRED WITHIN 2 TO 8 WEEKS OF TREATMENT INITIATION. HOWEVER, ISOLATED CASES HAVE BEEN REPORTED AFTER PROLONGED TREATMENT (E.G., 6 MONTHS). ACCORDINGLY, DURATION OF**

**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. LAMICTAL also displayed inhibitory

properties in the kindling model in rats both during kindling development and in the fully kindled state. 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 $\alpha_1$, $\alpha_2$, and $\beta$; 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). 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.

**Table 1. Mean* Pharmacokinetic Parameters in Healthy Volunteers and Adult Patients 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 carbamazepine, phenytoin, phenobarbital, or primidone† plus valproate: | | | | |
| Single-dose LAMICTAL | 25 | 3.8 (1.0-10.0) | 27.2 (11.2-51.6) | 0.53 (0.27-1.04) |
| Patients with epilepsy taking carbamazepine, phenytoin, phenobarbital, or primidone†: | | | | |
| Single-dose LAMICTAL | 24 | 2.3 (0.5-5.0) | 14.4 (6.4-30.4) | 1.10 (0.51-2.22) |
| Multiple-dose LAMICTAL | 17 | 2.0 (0.75-5.93) | 12.6 (7.5-23.1) | 1.21 (0.66-1.82) |

* 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.

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

***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 certain medications.** Because lamotrigine is metabolized predominantly by glucuronic acid conjugation, drugs that induce or inhibit glucuronidation may affect the apparent clearance of lamotrigine.

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

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

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

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

Coadministration of olanzapine did not have a clinically relevant effect on LAMICTAL pharmacokinetics (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 carbamazepine, phenytoin, phenobarbital, primidone, or rifampin.

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

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

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

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

| Pediatric Study Population | Number of Subjects | $T_{max}$ (h) | $t_{½}$ (h) | Cl/F (mL/min/kg) |
|---|---|---|---|---|
| **Ages 10 months-5.3 years** | | | | |
| Patients taking carbamazepine, phenytoin, phenobarbital, or primidone* | 10 | 3.0 (1.0-5.9) | 7.7 (5.7-11.4) | 3.62 (2.44-5.28) |
| Patients taking antiepileptic drugs (AEDs) with no known effect on the apparent clearance of lamotrigine | 7 | 5.2 (2.9-6.1) | 19.0 (12.9-27.1) | 1.2 (0.75-2.42) |
| Patients taking valproate only | 8 | 2.9 (1.0-6.0) | 44.9 (29.5-52.5) | 0.47 (0.23-0.77) |
| **Ages 5-11 years** | | | | |
| Patients taking carbamazepine, phenytoin, phenobarbital, or primidone* | 7 | 1.6 (1.0-3.0) | 7.0 (3.8-9.8) | 2.54 (1.35-5.58) |
| Patients taking carbamazepine, phenytoin, phenobarbital, or primidone* plus valproate | 8 | 3.3 (1.0-6.4) | 19.1 (7.0-31.2) | 0.89 (0.39-1.93) |
| Patients taking valproate only† | 3 | 4.5 (3.0-6.0) | 65.8 (50.7-73.7) | 0.24 (0.21-0.26) |
| **Ages 13-18 years** | | | | |
| Patients taking carbamazepine, | 11 | ‡ | ‡ | 1.3 |

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

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

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

‡ Parameter not estimated.

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

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

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

## 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 carbamazepine, phenytoin, phenobarbital, or primidone as the single antiepileptic drug (AED), 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 Carbamazepine, Phenytoin, Phenobarbital, or Primidone as the Single AED:*** 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).

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

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

**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 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 2 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, the generalized seizures of Lennox-Gastaut syndrome, and primary generalized tonic-clonic seizures in adults 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 carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single AED.

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

**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 1 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.

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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**Withdrawal Seizures:** As with other AEDs, LAMICTAL should not be abruptly discontinued. In patients with epilepsy there is a possibility of increasing seizure frequency. 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. Unless safety concerns require a more rapid withdrawal, the dose of LAMICTAL should be tapered over a period of at least 2 weeks (see DOSAGE AND ADMINISTRATION).

## PRECAUTIONS

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

**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.**

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

### 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 similar population at about the same time. Importantly, that drug is chemically unrelated to LAMICTAL. This evidence suggests, although it certainly does not prove, that the high SUDEP rates reflect population rates, not a drug effect.

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

### Use in Patients With Bipolar Disorder:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**Drug Interactions:**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

***Valproate:*** When LAMICTAL was administered to healthy volunteers (n = 18) receiving valproate, the trough steady-state valproate plasma concentrations 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 valproate plasma concentrations in either adult or pediatric patients in controlled clinical trials.

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

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

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

***Other:*** 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).

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

**Table 4. Summary of Drug Interactions With LAMICTAL**

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

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

* 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.

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

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

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

[¶] Slight decrease, not expected to be clinically relevant.

[#] Not administered, but an active metabolite of oxcarbazepine.

** Slight increase not expected to be clinically relevant.

↔ = 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: *Teratogenic Effects:*** 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.

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

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

**Pregnancy Exposure Registry:** To provide information regarding the effects of in utero exposure to LAMICTAL, physicians are advised to recommend that pregnant patients taking LAMICTAL enroll in the NAAED Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.
Physicians are also encouraged to register patients in the Lamotrigine Pregnancy Registry; enrollment in this registry must be done prior to any prenatal diagnostic tests and **before fetal outcome is known. Physicians** can obtain information by calling the Lamotrigine Pregnancy Registry at 1-800-336-2176 (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, breastfeeding while taking LAMICTAL is not recommended.
**Pediatric Use:** LAMICTAL is indicated as adjunctive therapy for partial seizures, the generalized seizures of Lennox-Gastaut syndrome, and primary generalized tonic-clonic seizures in patients above 2 years of age.

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 AEDs 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, coordination abnormality, dyspepsia, nausea, dizziness, rhinitis, anxiety, insomnia, infection, pain, weight decrease, chest pain, and dysmenorrhea. The most commonly observed (≥5%) adverse experiences associated with the use of LAMICTAL during the conversion to monotherapy (add-on) period, not seen at an equivalent frequency among low-dose valproate-treated patients, were dizziness, headache, nausea, asthenia, coordination abnormality, vomiting, rash, somnolence, diplopia, ataxia, accidental injury, tremor, blurred vision, insomnia, nystagmus, diarrhea, lymphadenopathy, pruritus, and sinusitis.

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

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

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

Approximately 11.5% of the 1,081 pediatric 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 (4.4%), reaction aggravated (1.7%), and ataxia (0.6%).

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

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

**Table 5. Treatment-Emergent Adverse Event Incidence in Placebo-Controlled Adjunctive Trials in Adult Patients With Epilepsy* (Events in at least 2% of patients treated with LAMICTAL and numerically more frequent than in the placebo group.)**

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

| | | |
|---|---|---|
| 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 of the following concomitant AEDs (carbamazepine, phenytoin, phenobarbital, or primidone) 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 6).

**Table 6. 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 7 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 7. 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,.

***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 8 lists adverse events that occurred in at least 2% of 339 pediatric patients with partial seizures or generalized seizures of Lennox-Gastaut syndrome, 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.

**Table 8. Treatment-Emergent Adverse Event Incidence in Placebo-Controlled Adjunctive Trials in Pediatric Patients With Epilepsy (Events in at least 2% of patients treated with LAMICTAL and numerically more frequent than in the placebo group.)**

| Body System/ Adverse Experience | Percent of Patients Receiving LAMICTAL (n = 168) | Percent of Patients Receiving Placebo (n = 171) |
|---|---|---|
| Body as a whole | | |
| Infection | 20 | 17 |
| Fever | 15 | 14 |
| Accidental injury | 14 | 12 |
| Abdominal pain | 10 | 5 |
| Asthenia | 8 | 4 |
| Flu syndrome | 7 | 6 |
| Pain | 5 | 4 |
| Facial edema | 2 | 1 |
| Photosensitivity | 2 | 0 |
| Cardiovascular | | |
| Hemorrhage | 2 | 1 |
| Digestive | | |
| Vomiting | 20 | 16 |
| Diarrhea | 11 | 9 |
| Nausea | 10 | 2 |

| | | |
|---|---|---|
| Constipation | 4 | 2 |
| Dyspepsia | 2 | 1 |
| Tooth disorder | 2 | 1 |
| Hemic and lymphatic | | |
| Lymphadenopathy | 2 | 1 |
| Metabolic and nutritional | | |
| Edema | 2 | 0 |
| Nervous system | | |
| Somnolence | 17 | 15 |
| Dizziness | 14 | 4 |
| Ataxia | 11 | 3 |
| Tremor | 10 | 1 |
| Emotional lability | 4 | 2 |
| Gait abnormality | 4 | 2 |
| Thinking abnormality | 3 | 2 |
| Convulsions | 2 | 1 |
| Nervousness | 2 | 1 |
| Vertigo | 2 | 1 |
| Respiratory | | |
| Pharyngitis | 14 | 11 |
| Bronchitis | 7 | 5 |
| Increased cough | 7 | 6 |
| Sinusitis | 2 | 1 |
| Bronchospasm | 2 | 1 |
| Skin | | |
| Rash | 14 | 12 |
| Eczema | 2 | 1 |
| Pruritus | 2 | 1 |
| Special senses | | |
| Diplopia | 5 | 1 |
| Blurred vision | 4 | 1 |
| Ear disorder | 2 | 1 |

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

**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 frequent than in placebo-treated patients are included in Table 9. Adverse events that occurred in at least 5% of patients and were numerically more common during the dose escalation phase of LAMICTAL in these trials (when patients may have been receiving concomitant medications) compared to the monotherapy phase were: headache (25%), rash (11%), dizziness (10%), diarrhea (8%), dream abnormality (6%), and pruritus (6%).

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

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

**Table 9. Treatment-Emergent Adverse Event Incidence in 2 Placebo-Controlled Trials in Adults With Bipolar I Disorder* (Events in at least 5% of patients treated with LAMICTAL monotherapy and numerically more frequent than in the placebo group.)**

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

* Patients in these studies were converted to LAMICTAL (100 to 400 mg/day) or placebo monotherapy from add-on therapy with other psychotropic medications. 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.

‡ In the overall 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 (see WARNINGS).

These adverse events were usually mild to moderate in intensity.

Other events that occurred in 5% or more patients but equally or more frequently in the placebo group included: dizziness, mania, headache, infection, influenza, pain, accidental injury, 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 patients 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, the generalized seizures of Lennox-Gastaut syndrome, and primary generalized tonic-clonic seizures 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 carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single AED.

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

**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.

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

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

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

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

See also DOSAGE AND ADMINISTRATION: Special Populations.

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

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

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

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

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

***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:**

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

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

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

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

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

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

| | For Patients Taking Valproate (see Table 11 for weight-based dosing guide) | For Patients Taking AEDs Other Than Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate* | For Patients Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone* and Not Taking Valproate |
|---|---|---|---|
| Weeks 1 and 2 | **0.15 mg/kg/day** in 1 or 2 divided doses, rounded down to the nearest whole tablet (see Table 11 for weight-based dosing guide). | **0.3 mg/kg/day** in 1 or 2 divided doses, rounded down to the nearest whole tablet. | **0.6 mg/kg/day** in 2 divided doses, rounded down to the nearest whole tablet. |
| Weeks 3 and 4 | **0.3 mg/kg/day** in 1 or 2 divided doses, rounded down to the nearest whole tablet (see Table 11 for weight-based dosing guide). | **0.6 mg/kg/day** in 2 divided doses, rounded down to the nearest whole tablet. | **1.2 mg/kg/day** in 2 divided doses, rounded down to the nearest whole tablet. |
| Weeks 5 onwards to maintenance | The dose should be increased every 1 to 2 weeks as follows: calculate 0.3 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily dose. | The dose should be increased every 1 to 2 weeks as follows: calculate 0.6 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily dose | The dose should be increased every 1 to 2 weeks as follows: calculate 1.2 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily |

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

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

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

**Table 11. The Initial Weight-Based Dosing Guide for Patients 2 to 12 Years Taking Valproate (Weeks 1 to 4) With Epilepsy**

| If the patient's weight is | | Give this daily dose, using the most appropriate combination of LAMICTAL 2-mg and 5-mg tablets | |
|---|---|---|---|
| Greater than | And less than | Weeks 1 and 2 | Weeks 3 and 4 |
| 6.7 kg | 14 kg | 2 mg every *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 |

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

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

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

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

***Conversion From Adjunctive Therapy With Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate as the Single AED 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 recommended maintenance dose of LAMICTAL as monotherapy is 500 mg/day given in 2 divided doses.

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

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

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

**Table 13. Conversion From Adjunctive Therapy With Valproate to Monotherapy With LAMICTAL in Patients ≥16 Years of Age With Epilepsy**

| | LAMICTAL | Valproate |
|---|---|---|
| Step 1 | Achieve a dose of 200 mg/day according to guidelines in Table 12 (if not already on 200 mg/day). | Maintain previous stable dose. |
| Step 2 | Maintain at 200 mg/day. | Decrease to 500 mg/day by decrements no greater than 500 mg/day per week and then maintain the dose of 500 mg/day for 1 week. |
| Step 3 | Increase to 300 mg/day and maintain for 1 week. | Simultaneously decrease to 250 mg/day and maintain for 1 week. |
| Step 4 | Increase by 100 mg/day every week to achieve maintenance dose of 500 mg/day. | Discontinue. |

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

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

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

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

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

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

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

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

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

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

| | For Patients Taking Valproate‡ | For Patients Not Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Rifampin† and Not Taking Valproate‡ | For Patients Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Rifampin† and Not Taking Valproate‡ |
|---|---|---|---|
| Weeks 1 and 2 | 25 mg every *other* day | 25 mg daily | 50 mg daily |
| Weeks 3 and 4 | 25 mg daily | 50 mg daily | 100 mg daily, in divided doses |
| Week 5 | 50 mg daily | 100 mg daily | 200 mg daily, in divided |

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

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

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

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

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

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

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

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

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

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

***Discontinuation Strategy in Bipolar Disorder:*** As with other AEDs, LAMICTAL should not be abruptly discontinued. In the controlled clinical trials, there was no increase in the incidence, type, or severity of adverse experiences following abrupt termination of LAMICTAL. 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. Discontinuation of LAMICTAL should involve a step-wise reduction of dose over at least 2 weeks (approximately 50% per week) unless safety concerns require a more rapid withdrawal.

**Administration of LAMICTAL Chewable Dispersible Tablets:** LAMICTAL Chewable Dispersible Tablets may be swallowed whole, chewed, or dispersed 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). Approximately 1 minute later, when the tablets are completely dispersed, swirl the solution and consume the entire quantity immediately. *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 Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Rifampin 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 0173-0594-01)

**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 Carbamazepine, Phenytoin, Phenobarbital, Primidone, Rifampin, or 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 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 accompanying the product.

# MEDICATION GUIDE

## LAMICTAL (la-MIK-tal)
## (lamotrigine)
## Tablets
## Chewable Dispersible Tablets

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

### What is the most important information I should know about LAMICTAL?

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

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

The risk of getting a rash is higher if you:

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

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

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

- **a skin rash**
- **hives**
- **fever**
- **swollen lymph glands**
- **painful sores in the mouth or around your eyes**
- **swelling of your lips or tongue**
- **yellowing of your skin or eyes**
- **unusual bruising or bleeding**
- **severe fatigue or weakness**
- **severe muscle pain**

- **frequent infections**

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

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

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

- thoughts about suicide or dying
- attempt to commit suicide
- new or worse depression
- new or worse anxiety
- feeling agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

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

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

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

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

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

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

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

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

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

**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** |

## What is LAMICTAL?

LAMICTAL is a prescription medicine used:

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

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

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

## Who should not take LAMICTAL?

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

### What should I tell my healthcare provider before taking LAMICTAL?

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

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

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

### How should I take LAMICTAL?

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

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

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

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

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

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

- See "What is the most important information I should know about LAMICTAL?"

Common side effects of LAMICTAL include:

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

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

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

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

**How should I store LAMICTAL?**

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

**General information about LAMICTAL**

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

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

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

**What are the ingredients in LAMICTAL?**

**LAMICTAL Tablets**

Active ingredient: lamotrigine.

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

**LAMICTAL Chewable Dispersible Tablets**

Active ingredient: lamotrigine.

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

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

(Date of Issue)

LMT: XMG


Manufactured for

GlaxoSmithKline

Research Triangle Park, NC 27709

by DSM Pharmaceuticals, Inc.

Greenville, NC 27834 or

GlaxoSmithKline

Research Triangle Park, NC 27709

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



April 2009

LMT:1MG

# NDA 20-241 Lamictal (lamotrigine) Tablets

# NDA 20-764 Lamictal (lamotrigine) Chewable Dispersible Tablets

## RISK EVALUATION AND MITIGATION STRATEGY (REMS)

### I. GOAL:

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

### II. REMS ELEMENTS

### A. Medication Guide

A Medication Guide will be dispensed with each LAMICTAL prescription.

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

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

### B. Communication Plan

Not applicable.

### C. Elements to Assure Safe Use

Not applicable.

### D. Implementation System

Not applicable.

### III. Timetable for Submission of Assessments

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

# APPENDIX 1: Specifications and Justification for Supply of Medication Guide

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

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

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

   **Dispense the enclosed Medication Guide to each patient.**

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

   **Dispense the accompanying Medication Guide to each patient.**

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

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

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

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

†Inpatient Use Only (exempt)

# APPENDIX 2: REMS Assessments

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

The following assessments are planned:

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

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