CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020241/S003 AND 020764/S001

FINAL PRINTED LABELING

LAMICTAL®
(lamotrigine)
Tablets

PRODUCT INFORMATION

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 1% (1/100) IN PEDIATRIC PATIENTS (AGE <16 YEARS) AND 0.3% (3/1000) IN ADULTS. IN WORLDWIDE POSTMARKETING EXPERIENCE, RARE CASES OF TOXIC EPIDERMAL NECROLYSIS AND/OR RASH-RELATED DEATH HAVE BEEN REPORTED, BUT THEIR NUMBERS ARE TOO FEW TO PERMIT A PRECISE ESTIMATE OF THE RATE.

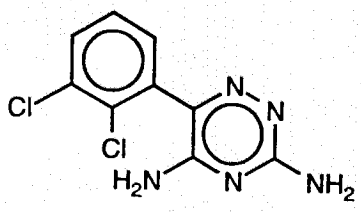
BECAUSE THE RATE OF SERIOUS RASH IS GREATER IN PEDIATRIC PATIENTS THAN IN ADULTS, IT BEARS EMPHASIS THAT LAMICTAL IS APPROVED ONLY FOR USE IN PEDIATRIC PATIENTS BELOW THE AGE OF 16 YEARS WHO HAVE SEIZURES ASSOCIATED WITH THE LENNOX-GASTAUT SYNDROME (SEE INDICATIONS).

OTHER THAN AGE, THERE ARE AS YET NO FACTORS IDENTIFIED THAT ARE KNOWN TO PREDICT THE RISK OF OCCURRENCE OR THE SEVERITY OF RASH ASSOCIATED WITH LAMICTAL. THERE ARE SUGGESTIONS, YET TO BE PROVEN, THAT THE RISK OF RASH MAY ALSO BE INCREASED BY 1) COADMINISTRATION OF LAMICTAL WITH VALPROIC ACID (VPA), 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 5 mg (white) or 25 mg (white) of lamotrigine and the following inactive ingredients: blackcurrant flavor, calcium carbonate, low-substituted hydroxypropylcellulose, magnesium aluminum silicate, magnesium stearate, povidone, saccharin sodium, and sodium starch glycolate.

CLINICAL PHARMACOLOGY:

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

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

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

on dihydropyridine-sensitive calcium channels. It had weak effects at sigma opioid receptors (IC_{50} = 145 μM). Lamotrigine did not inhibit the uptake of norepinephrine, dopamine, serotonin, or aspartic acid (IC_{50}>100 μM).

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

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

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

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

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

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

Table 1: Mean* Pharmacokinetic Parameters in Adult Patients With Epilepsy or Healthy Volunteers

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)
Patients taking enzyme-inducing antiepileptic drugs (EIAEDs)†:				
Single-dose LAMICTAL	24	2.3 (0.5-5.0)	14.4 (6.4-30.4)	1.10 (0.51-2.22)
Multiple-dose LAMICTAL	17	2.0 (0.75-5.93)	12.6 (7.5-23.1)	1.21 (0.66-1.82)
Patients taking EIAEDs + VPA:				
Single-dose LAMICTAL	25	3.8 (1.0-10.0)	27.2 (11.2-51.6)	0.53 (0.27-1.04)
Patients taking VPA only:				
Single-dose LAMICTAL	4	4.8 (1.8-8.4)	58.8 (30.5-88.8)	0.28 (0.16-0.40)
Healthy volunteers taking VPA:				
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)
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)

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

†Examples of EIAEDs are carbamazepine, phenobarbital, phenytoin, and primidone.

The apparent clearance of lamotrigine is affected by the coadministration of AEDs.

Lamotrigine is eliminated more rapidly in patients who have been taking hepatic EIAEDs, including carbamazepine, phenytoin, phenobarbital, and primidone. Most clinical experience is derived from this population.

VPA, however, actually decreases the apparent clearance of lamotrigine (i.e., more than doubles the elimination half-life of lamotrigine), whether given with or without EIAEDs. Accordingly, if lamotrigine is to be administered to a patient receiving VPA, lamotrigine must be given at a reduced dosage, less than half the dose used in patients not receiving VPA (see DOSAGE AND ADMINISTRATION 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 four to six 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 VPA. 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 six 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%).

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

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

Dose Proportionality: In healthy volunteers not receiving any other medications and given single doses, the plasma concentrations of lamotrigine increased in direct proportion to the dose

administered over the range of 50 to 400 mg. In two 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 six 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 pharmacokinetic parameters of lamotrigine in patients with impaired liver function have not been studied.

Age: Pediatric Patients: The pharmacokinetics of LAMICTAL following a single 2-mg/kg dose were evaluated in two studies of pediatric patients with epilepsy (n = 25 for patients aged 10 months to 5.3 years and n = 19 for patients aged 5 to 11 years). All patients were receiving concomitant therapy with other AEDs. Lamotrigine pharmacokinetic parameters for pediatric patients are summarized in Table 2.

As with adults, the elimination of lamotrigine in pediatric patients was similarly affected by concomitant AEDs. Weight normalized oral clearance (Cl/F) was higher (onefold to threefold) in infants and children (age 10 months to 11 years) than in the adolescents and adults, while adolescents and adults had similar mean values of Cl/F.

186 187 **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 EIAEDs	10	3.0 (1.0-5.9)	7.7 (5.7-11.4)	3.62 (2.44-5.28)
Patients taking AEDs with no known effect on drug-metabolizing enzymes	7	5.2 (2.9-6.1)	19.0 (12.9-27.1)	1.2 (0.75-2.42)
Patients taking VPA only	8	2.9 (1.0-6.0)	44.9 (29.5-52.5)	0.47 (0.23-0.77)
Ages 5-11 years				
Patients taking EIAEDs	7	1.6 (1.0-3.0)	7.0 (3.8-9.8)	2.54 (1.35-5.58)
Patients taking EIAEDs plus VPA	8	3.3 (1.0-6.4)	19.1 (7.0-31.2)	0.89 (0.39-1.93)
Patients taking VPA only*	3	4.5 (3.0-6.0)	65.8 (50.7-73.7)	0.24 (0.21-0.26)
Ages 13-18 years				
Patients taking EIAEDs	11	†	†	1.3
Patients taking EIAEDs plus VPA	8	†	†	0.5
Patients taking VPA only	4	†	†	0.3

188 *Two subjects were included in the calculation for mean t_{max}.
189 †Parameter not estimated.
190
191 ***Elderly:*** In a single-dose study (150 mg of LAMICTAL), the pharmacokinetics of lamotrigine in
192 12 elderly volunteers between the ages of 65 and 76 years (mean creatinine clearance = 61 mL/min,
193 range = 33 to 108) were similar to those of young, healthy volunteers in other studies.
194 ***Gender:*** The clearance of lamotrigine is not affected by gender.
195 ***Race:*** The apparent oral clearance of lamotrigine was 25% lower in non-Caucasians than
196 Caucasians.
197
198 **CLINICAL STUDIES:** The results of controlled clinical trials established the efficacy of LAMICTAL as
199 monotherapy in adults with partial onset seizures already receiving treatment with a single enzyme
200 inducing anti-epileptic drug (EIAED), as adjunctive therapy in adults with partial seizures, and as
201 adjunctive therapy in the generalized seizures of Lennox-Gastaut syndrome in pediatric and adult
202 patients.

Monotherapy With LAMICTAL in adults with partial seizures already receiving treatment with a single enzyme inducing anti-epileptic drug (EIAED): The effectiveness of monotherapy with LAMICTAL was established in a multicenter, double-blind clinical trial enrolling 156 adult outpatients with partial seizures. The patients experienced at least four simple partial, complex partial, and/or secondarily generalized seizures during each of two consecutive 4-week periods while receiving carbamazepine or phenytoin monotherapy during baseline. LAMICTAL (target dose of 500 mg/day) or VPA (1000 mg/day) was added to either carbamazepine or phenytoin monotherapy over a 4-week period. Patients were then converted to monotherapy with LAMICTAL or VPA 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 VPA 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: The effectiveness of LAMICTAL as adjunctive therapy (added to other AEDs) was established in three 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 three 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 two other anticonvulsants and VPA 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 two other anticonvulsants and VPA 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 two other anticonvulsants. Thirteen patients were on concomitant VPA; 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 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 three drugs. Patients were dosed on a fixed-dose regimen based on body weight and VPA use. Target doses were designed to approximate 5 mg/kg per day for patients taking VPA (maximum dose, 200 mg/day) and 15 mg/kg per day for patients not taking VPA (maximum dose, 400 mg/day). The primary efficacy endpoint was median reduction 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).

INDICATIONS AND USAGE:

Adjunctive Use: LAMICTAL is indicated as adjunctive therapy in adults with partial seizures and as adjunctive therapy in the generalized seizures of Lennox-Gastaut syndrome in pediatric and adult patients.

Monotherapy Use: LAMICTAL is indicated for conversion to monotherapy in adults with partial seizures who are receiving treatment with a single enzyme inducing anti-epileptic drug (EIAED).

Safety and effectiveness of LAMICTAL have not been established 1) as initial monotherapy, 2) for

conversion to monotherapy from non-enzyme-inducing AEDs (e.g., valproate), or 3) for simultaneous conversion to monotherapy from two or more concomitant AEDs (see DOSAGE AND ADMINISTRATION).

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

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.

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Serious Rash: ***Pediatric Population:*** The incidence of serious rash associated with hospitalization and discontinuation of LAMICTAL in a prospectively followed cohort of pediatric patients was approximately 1.1% (14/1233). When these 14 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 were no deaths or permanent sequelae in these patients. Additionally, there have been rare cases of toxic epidermal necrolysis with and without permanent sequelae and/or death in US and foreign postmarketing experience. It bears emphasis, accordingly, that LAMICTAL is only approved for use in those patients below the age of 16 who have seizures associated with the Lennox-Gastaut syndrome (see INDICATIONS).

Because foreign postmarketing reports suggested that the rate of serious rash was greater with concomitant VPA use and because metabolism of LAMICTAL is inhibited by VPA, resulting in increased LAMICTAL plasma levels, the drug development database was examined for concomitant VPA use. In pediatric patients who used VPA concomitantly, 1.1% (5/443) experienced a serious rash compared to 1% (6/628) patients not taking VPA. Although the numbers are small, 1.7% (5/294) patients taking either VPA alone or VPA + non-EIAEDs experienced a serious rash compared to 0% (0/149) patients taking VPA + EIAEDs.

Adult Population: Serious rash associated with hospitalization and discontinuation of LAMICTAL occurred in 0.3% (11/3348) of patients who received LAMICTAL in premarketing clinical trials. 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 VPA in a multidrug regimen increases the risk of serious, potentially life-threatening rash in adults. Specifically, of 584 patients administered LAMICTAL with VPA in clinical trials, 6 (1%) were hospitalized in association with rash; in contrast, 4 (0.16%) of 2398 clinical trial patients and volunteers administered LAMICTAL in the absence of VPA were hospitalized.

Other examples of serious and potentially life-threatening rash that did not lead to hospitalization also occurred in premarketing development. Among these, one 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 dysfunction such as 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: Fatalities associated with multiorgan failure and various degrees of hepatic failure have been reported in 2/3796 adult patients and 3/1136 pediatric patients who received LAMICTAL during premarketing clinical trials. Rare fatalities from multiorgan failure have also been reported in compassionate plea and postmarketing use. All of these cases occurred in association with other serious medical events (e.g., status epilepticus, overwhelming sepsis), making it impossible to identify the initiating cause.

Additionally, three 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 two patients. Both pediatric patients were receiving concomitant therapy with VPA, while the adult patient was being treated with carbamazepine and clonazepam. All patients subsequently recovered with supportive care after treatment with LAMICTAL was discontinued.

Pure Red Cell Aplasia (PRCA): A case of PRCA was reported in a 32-year-old male with a history of β-thalassemia. The patient had a microcytic anemia (hemoglobin 11 g/dL) that was stable while the patient received carbamazepine but became more severe in the 3 months after LAMICTAL was added. A bone marrow aspirate revealed markedly decreased erythropoiesis but normal granulopoiesis and thrombopoiesis. Erythropoiesis resumed after discontinuation of LAMICTAL and

transfusions of packed red cells. Although PRCA is known to occur in patients with hemoglobinopathies, it is not known if β-thalassemia is a specific risk factor for the development of PRCA.

Withdrawal Seizures: As a rule, AEDs should not be abruptly discontinued because of the possibility of increasing seizure frequency. 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).

Special Dosing Considerations for Pediatric Patients: The lowest available strength of LAMICTAL Chewable Dispersible Tablets is 5 mg, and only whole tablets should be administered. Since the dosing of LAMICTAL in pediatric patients is based on body weight and the lowest tablet strength is 5 mg, some low-weight pediatric patients should not receive LAMICTAL. Specifically, pediatric patients who weigh less than 17 kg (37 lb) should not receive LAMICTAL because therapy cannot be initiated using the dosing guidelines and the currently available tablet strengths (see DOSAGE AND ADMINISTRATION).

PRECAUTIONS:

Dermatological Events (see BOX WARNING, WARNINGS): Serious rashes associated with hospitalization and discontinuation of LAMICTAL have been reported. Rare deaths have been reported, but their numbers are too few to permit a precise estimate of the rate. There are suggestions, yet to be proven, that the risk of rash may also be increased by 1) coadministration of LAMICTAL with VPA, 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 clinical trials, approximately 10% of all 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.**

Sudden Unexplained Death in Epilepsy (SUDEP): During the premarketing development of LAMICTAL, 20 sudden and unexplained deaths were recorded among a cohort of 4700 patients with epilepsy (5747 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 2343 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.

Addition of LAMICTAL to a Multidrug Regimen That Includes VPA (Dosage Reduction): Because VPA reduces the clearance of lamotrigine, the dosage of lamotrigine in the presence of VPA 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 no 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.

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 physician if worsening of seizure control occurs.

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 breast-feeding an infant.

Patients should be informed of the availability of a patient information leaflet, and they should be instructed to read the leaflet prior to taking LAMICTAL. See PATIENT INFORMATION at the end of this labeling for the text of the leaflet 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 AEDs being taken concomitantly (see Table 3), monitoring of the plasma levels of LAMICTAL and concomitant AEDs may be indicated, particularly during dosage adjustments. In general, clinical judgment should be exercised regarding monitoring of plasma levels of LAMICTAL and other anti-seizure drugs and whether or not dosage adjustments are necessary.

Drug Interactions: ***Antiepileptic Drugs:*** The use of AEDs in combination is complicated by the potential for pharmacokinetic interactions.

The interaction of lamotrigine with phenytoin, carbamazepine, and VPA has been studied. The net effects of these various AED combinations on individual AED plasma concentrations are summarized in Table 3.