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 Clinical Pharmacology (12.3)]*. 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).

12.3 Pharmacokinetics

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 14 and 16.

Table 14. Mean[a] Pharmacokinetic Parameters in Healthy Volunteers and Adult Patients With Epilepsy

Adult Study Population	Number of Subjects	T_{max}: Time of Maximum Plasma Concentration (hr)	$t_{½}$: Elimination Half-life (hr)	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[b] 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:[b]				
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)

[a]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.

[b]Carbamazepine, phenobarbital, phenytoin, and primidone have been shown to increase the apparent clearance of lamotrigine. Estrogen-containing oral contraceptives and other drugs such as rifampin that induce lamotrigine glucuronidation have also been shown to increase the apparent clearance of lamotrigine *[see Drug Interactions (7)]*.

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. In terms of rate and extent of absorption, lamotrigine orally disintegrating tablets whether disintegrated in the mouth or swallowed whole with water were equivalent to the lamotrigine compressed tablets swallowed with water.

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.

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.

Metabolism: 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%).

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 with values obtained in the same volunteers following a single dose. Evidence gathered from other sources suggests that self-induction by lamotrigine may not occur when lamotrigine is given as adjunctive therapy in patients receiving enzyme-inducing drugs such as carbamazepine, phenytoin, phenobarbital, primidone, or drugs such as rifampin that induce lamotrigine glucuronidation *[see Drug Interactions (7)]*.

Elimination: The elimination half-life and apparent clearance of lamotrigine following administration of LAMICTAL to adult patients with epilepsy and healthy volunteers is summarized in Table 14. Half-life and apparent oral clearance vary depending on concomitant AEDs.

Drug Interactions: The apparent clearance of lamotrigine is affected by the coadministration of certain medications *[see Warnings and Precautions (5.8, 5.12), Drug Interactions (7)]*.

The net effects of drug interactions with LAMICTAL are summarized in Tables 13 and 15, followed by details of the drug interaction studies below.

Table 15. Summary of Drug Interactions With LAMICTAL

Drug	Drug Plasma Concentration With Adjunctive LAMICTAL[a]	Lamotrigine Plasma Concentration With Adjunctive Drugs[b]
Oral contraceptives (e.g., ethinylestradiol/levonorgestrel)[c]	↔[d]	↓
Bupropion	Not assessed	↔
Carbamazepine (CBZ)	↔	↓
CBZ epoxide[e]	?	
Felbamate	Not assessed	↔
Gabapentin	Not assessed	↔
Levetiracetam	↔	↔
Lithium	↔	Not assessed
Olanzapine	↔	↔[f]
Oxcarbazepine	↔	↔
10-monohydroxy oxcarbazepine metabolite[g]	↔	
Phenobarbital/primidone	↔	↓
Phenytoin (PHT)	↔	↓
Pregabalin	↔	↔
Rifampin	Not assessed	↓
Topiramate	↔[h]	↔
Valproate	↓	↑
Valproate + PHT and/or CBZ	Not assessed	↔
Zonisamide	Not assessed	↔

[a]From adjunctive clinical trials and volunteer studies.

[b]Net effects were estimated by comparing the mean clearance values obtained in adjunctive clinical trials and volunteer studies.

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

[d]Modest decrease in levonorgestrel.

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

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

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

[h]Slight increase, not expected to be clinically relevant.

↔ = No significant effect.

? = Conflicting data.

Estrogen-Containing 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 mean decreases 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 with 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 other drugs such as rifampin that induce lamotrigine glucuronidation *[see Drug Interactions (7)]*). 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 reactions.

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 were mean decreases 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 may be necessary for women receiving estrogen-containing oral contraceptive preparations *[see Dosage and Administration (2.1)]*.

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 daily) 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 lamotrigine than in patients receiving other AEDs with lamotrigine *[see Adverse Reactions (6.1)]*. The mechanism of this interaction is unclear. The effect of lamotrigine on plasma concentrations of carbamazepine-epoxide is unclear. In a small subset of patients (n = 7) studied in a placebo-controlled trial, lamotrigine 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 lamotrigine (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 lamotrigine both with and without gabapentin, gabapentin does not appear to change the apparent clearance of lamotrigine.

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

Lithium: The pharmacokinetics of lithium were not altered in healthy subjects (n = 20) by coadministration of lamotrigine (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 lamotrigine (200 mg once daily) in healthy male volunteers (n = 16) compared with 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 were reduced on average by 24% and 20%, respectively, following the addition of olanzapine to lamotrigine in healthy male volunteers compared with those receiving lamotrigine 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 lamotrigine (200 mg once daily) in healthy male volunteers (n = 13) compared with 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 with those receiving LAMICTAL alone. Limited clinical data suggest a higher incidence of headache, dizziness, nausea, and somnolence with coadministration of lamotrigine and oxcarbazepine compared with lamotrigine alone or oxcarbazepine alone.

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

Phenytoin: Lamotrigine 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 lamotrigine 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 lamotrigine by approximately 2-fold (AUC decreased by approximately 40%).

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

Valproate: When lamotrigine 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 lamotrigine 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 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 lamotrigine (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 lamotrigine. 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 lamotrigine 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.

Results of in vitro experiments suggest that lamotrigine does not reduce the clearance of drugs eliminated predominantly by CYP2D6.

Special Populations:*Patients With Renal Impairment:* 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 lamotrigine. 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 with 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 *[see Dosage and Administration (2.1)]*.

Hepatic Disease: The pharmacokinetics of lamotrigine following a single 100-mg dose of lamotrigine were evaluated in 24 subjects with mild, moderate, and severe hepatic impairment (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 clearances of lamotrigine in patients with mild (n = 12), moderate (n = 5), severe without ascites (n = 2), and severe with ascites (n = 5) liver impairment were 0.30 ± 0.09, 0.24 ± 0.1, 0.21 ± 0.04, and 0.15 ± 0.09 mL/min/kg, respectively, as compared with 0.37 ± 0.1 mL/min/kg in the healthy controls. Mean half-lives of lamotrigine in patients with mild, moderate, severe without ascites, and severe with ascites hepatic impairment were 46 ± 20, 72 ± 44, 67 ± 11, and 100 ± 48 hours, respectively, as compared with 33 ± 7 hours in healthy controls *[see Dosage and Administration (2.1)]*.

Age:Pediatric Patients: The pharmacokinetics of lamotrigine following a single 2-mg/kg dose were evaluated in 2 studies of pediatric patients (n = 29 for patients 10 months to 5.9 years of age and n = 26 for patients 5 to 11 years of age). Forty-three patients received concomitant therapy with other AEDs and 12 patients received lamotrigine as monotherapy. Lamotrigine pharmacokinetic parameters for pediatric patients are summarized in Table 16.

Population pharmacokinetic analyses involving patients 2 to 18 years of age 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 (2.2)]*. 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 16. Mean Pharmacokinetic Parameters in Pediatric Patients With Epilepsy

Pediatric Study Population	Number of Subjects	T_{max} (hr)	$t_{½}$ (hr)	Cl/F (mL/min/kg)
Ages 10 months-5.3 years				
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone[a]	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 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[a]	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[a] 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[b]	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, phenytoin, phenobarbital, or primidone[a]	11	[c]	[c]	1.3
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone[a] plus valproate	8	[c]	[c]	0.5
Patients taking valproate only	4	[c]	[c]	0.3

[a]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 Drug Interactions (7)]*.

[b]Two subjects were included in the calculation for mean T_{max}.

[c]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.

13 NONCLINICAL TOXICOLOGY

13.1 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/day for mice and 10 to 15 mg/kg/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/day or 0.4 times the human dose on a mg/m^2 basis. The effect of lamotrigine on human fertility is unknown.

14 CLINICAL STUDIES

14.1 Epilepsy

Monotherapy With LAMICTAL in Adults With Partial Seizures Already Receiving Treatment With Carbamazepine, Phenytoin, Phenobarbital, or Primidone as the Single Antiepileptic Drug: 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 seizures. The primary efficacy variable was the proportion of patients in each treatment group who met escape criteria.

The percentages of patients who met escape criteria were 42% (32/76) in the group receiving LAMICTAL 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 with 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 with 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 with 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 2 to 16 years of age (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/day for patients taking valproate (maximum dose: 250 mg/day) and 15 mg/kg/day for the patients not taking valproate (maximum dose: 750 mg/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 3 to 25 years of age (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/day for patients taking valproate (maximum dose: 200 mg/day) and 15 mg/kg/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 with 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 ($P = 0.006$).

14.2 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 dose of LAMICTAL 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

LAMICTAL (lamotrigine) 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.

100 mg, peach, scored, shield-shaped tablets debossed with “LAMICTAL” and “100”, bottles of 100 (NDC 0173-0642-55).

150 mg, cream, scored, shield-shaped tablets debossed with “LAMICTAL” and “150”, bottles of 60 (NDC 0173-0643-60).

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 (lamotrigine) Starter Kit for Patients Taking Valproate (Blue Kit)

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 (lamotrigine) Starter Kit for Patients Taking Carbamazepine, Phenytoin, Phenobarbital, or Primidone and Not Taking Valproate (Green Kit)

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 98 tablets (84/25-mg tablets and 14/100-mg tablets) (NDC 0173-0817-28).

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 (lamotrigine) Starter Kit for Patients Not Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate (Orange Kit)

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 49 tablets (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.

LAMICTAL (lamotrigine) 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.

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

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 ODT (lamotrigine) Orally Disintegrating Tablets

25 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with "LMT" on one side and "25" on the other, Maintenance Packs of 30 (NDC 0173-0772-02).

50 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with "LMT" on one side and "50" on the other, Maintenance Packs of 30 (NDC 0173-0774-02).

100 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with "LAMICTAL" on one side and "100" on the other, Maintenance Packs of 30 (NDC 0173-0776-02).

200 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with "LAMICTAL" on one side and "200" on the other, Maintenance Packs of 30 (NDC 0173-0777-02).

Store between 20°C to 25°C (68°F to 77°F); with excursions permitted between 15°C and 30°C (59°F and 86°F).

LAMICTAL ODT (lamotrigine) Patient Titration Kit for Patients Taking Valproate (Blue ODT Kit)

25 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with "LMT" on one side and "25" on the other, and 50 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with "LMT" on one side and "50" on the other, blisterpack of 28 tablets (21/25-mg tablets and 7/50-mg tablets) (NDC 0173-0779-00).

LAMICTAL ODT (lamotrigine) Patient Titration Kit for Patients Taking Carbamazepine, Phenytoin, Phenobarbital, or Primidone and Not Taking Valproate (Green ODT Kit)

50 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with "LMT" on one side and "50" on the other, and 100 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with "LAMICTAL" on one side and "100" on the other, blisterpack of 56 tablets (42/50-mg tablets and 14/100-mg tablets) (NDC 0173-0780-00).

LAMICTAL ODT (lamotrigine) Patient Titration Kit for Patients Not Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate (Orange ODT Kit)

25 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with "LMT" on one side and "25" on the other, 50 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with "LMT" on one side and "50" on the other, and 100 mg, white to off-white, round, flat-faced, radius edge, tablets debossed with "LAMICTAL" on one side and "100" on the other, blisterpack of 35 (14/25-mg tablets, 14/50-mg tablets, and 7/100-mg tablets) (NDC 0173-0778-00).

Store between 20°C to 25°C (68°F to 77°F); with excursions permitted between 15°C and 30°C (59°F and 86°F).

Blisterpacks: If the product is dispensed in a blisterpack, the patient should be advised to examine the blisterpack before use and not use if blisters are torn, broken, or missing.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

17.1 Rash

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.

17.2 Multiorgan Hypersensitivity Reactions, Blood Dyscrasias, and Organ Failure

Patients should be instructed that multiorgan hypersensitivity reactions and acute multiorgan failure may occur with LAMICTAL. Isolated organ failure or isolated blood dyscrasias without evidence of multiorgan hypersensitivity may also occur. Patients should contact their physician immediately if they

experience any signs or symptoms of these conditions *[see Warnings and Precautions (5.2, 5.3)]*.

17.3 Suicidal Thinking and Behavior

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.

17.4 Worsening of Seizures

Patients should be advised to notify their physician if worsening of seizure control occurs.

17.5 Central Nervous System Adverse Effects

Patients should be advised that LAMICTAL may cause dizziness, somnolence, and other symptoms and signs of 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.

17.6 Pregnancy and Nursing

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 breastfeed or are breastfeeding an infant.

Patients should also be encouraged to enroll in the 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 Use in Specific Populations (8.1)]*.

Patients who intend to breastfeed should be informed that LAMICTAL is present in breast milk and that they should monitor their child for potential adverse effects of this drug. Benefits and risks of continuing breastfeeding should be discussed with the patient.

17.7 Oral Contraceptive Use

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 Warnings and Precautions (5.8), Clinical Pharmacology (12.3)]*. Women should also be advised to promptly notify their physician if they experience adverse reactions or changes in menstrual pattern (e.g., break-through bleeding) while receiving LAMICTAL in combination with these medications.

17.8 Discontinuing LAMICTAL

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.

17.9 Aseptic Meningitis

Patients should be advised that LAMICTAL may cause aseptic meningitis. Patients should be advised to notify their physician immediately if they develop signs and symptoms of meningitis such as headache, fever, nausea, vomiting, stiff neck, rash, abnormal sensitivity to light, myalgia, chills, confusion, or drowsiness while taking LAMICTAL.

17.10 Potential Medication Errors

Medication errors involving LAMICTAL have occurred. In particular the names LAMICTAL or lamotrigine can be confused with the names of other commonly used medications. Medication errors may also occur between the different formulations of LAMICTAL. To reduce the potential of medication errors, write and say LAMICTAL clearly. Depictions of the LAMICTAL Tablets, Chewable Dispersible Tablets, and Orally Disintegrating Tablets can be found in the Medication Guide that accompanies the product to highlight the distinctive markings, colors, and shapes that serve to identify the different presentations of the drug and thus may help reduce the risk of medication errors. **To avoid a medication error of using the wrong drug or formulation, patients should be strongly advised to visually inspect their tablets to verify that they are LAMICTAL, as well as the correct formulation of LAMICTAL, each time they fill their prescription** *[see Dosage Forms and Strengths (3.1, 3.2, 3.3), How Supplied/Storage and Handling (16)].*

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Microcaps and AdvaTab are registered trademarks of Eurand, Inc.

GlaxoSmithKline

Research Triangle Park, NC 27709

LAMICTAL Tablets and Chewable Dispersible Tablets are manufactured by

DSM Pharmaceuticals, Inc., Greenville, NC 27834 or

GlaxoSmithKline, Research Triangle Park, NC 27709

LAMICTAL Orally Disintegrating Tablets are manufactured by

Eurand, Inc., Vandalia, OH 45377

LMT:8PI

MEDICATION GUIDE

LAMICTAL® (la-MIK-tal)

(lamotrigine)

Tablets and Chewable Dispersible Tablets

LAMICTAL® ODT™

(lamotrigine)

Orally Disintegrating 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 even cause death.

There is no way to tell if a mild rash will become more serious. A serious skin rash can happen at any time during your treatment with LAMICTAL, but is more likely to happen within the first 2 to 8 weeks of treatment. Children between 2 to 16 years of age have a higher chance of getting this serious skin rash while taking LAMICTAL.

The risk of getting a serious skin 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.

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

- **a skin rash**
- **blistering or peeling of your skin**
- **hives**
- **painful sores in your mouth or around your eyes**

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

2. Other serious reactions, including serious blood problems or liver problems. LAMICTAL can also cause other types of allergic reactions or serious problems that may affect organs and other parts of your body like your 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 these symptoms:

- fever
- frequent infections
- severe muscle pain
- swelling of your face, eyes, lips, or tongue
- swollen lymph glands
- unusual bruising or bleeding
- weakness, fatigue
- yellowing of your skin or the white part of your eyes

3. 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.

4. LAMICTAL may rarely cause aseptic meningitis, a serious inflammation of the protective membrane that covers the brain and spinal cord.

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

- headache
- fever
- nausea
- vomiting
- stiff neck
- rash
- unusual sensitivity to light
- muscle pains
- chills
- confusion
- drowsiness

Meningitis has many causes other than LAMICTAL, which your doctor would check for if you developed meningitis while taking LAMICTAL.

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?"

5. 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, Chewable Dispersible Tablets, and Orally Disintegrating 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

LAMICTAL ODT (lamotrigine) Orally Disintegrating Tablets

25 mg, white to off-white
Imprinted with LMT on one side
25 on the other

50 mg, white to off-white
Imprinted with
LMT on one side
50 on the other

100 mg, white to off-white
Imprinted with
LAMICTAL on one side
100 on the other

200 mg, white to off-white
Imprinted with
LAMICTAL
on one side
200 on the other

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.
- have had aseptic meningitis after taking LAMICTAL or LAMICTAL XR (lamotrigine).
- 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 these medicines may cause side effects (such as dizziness, lack of coordination, or double vision). Starting these medicines may 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 passes into breast milk and may cause side effects in a breastfed baby. If you breastfeed while taking LAMICTAL, watch your baby closely for trouble breathing, episodes of temporarily stopping breathing, sleepiness, or poor sucking. Call your baby's healthcare provider right away if you see any of these problems. Talk to your healthcare provider about the best way to feed your baby if you take LAMICTAL.

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. If you use LAMICTAL with certain other medicines, they 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.
- If you have trouble swallowing LAMICTAL tablets, tell your healthcare provider because there may be another form of LAMICTAL you can take.
- LAMICTAL ODT should be placed on the tongue and moved around the mouth. The tablet will rapidly disintegrate, can be swallowed with or without water, and can be taken with or without food.
- 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.

- If you receive LAMICTAL in a blisterpack, examine the blisterpack before use. Do not use if blisters are torn, broken, or missing.

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.

LAMICTAL ODT Orally Disintegrating Tablets

Active ingredient: lamotrigine

Inactive ingredients: artificial cherry flavor, crospovidone, ethylcellulose, magnesium stearate, mannitol, polyethylene, and sucralose.

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

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GlaxoSmithKline

Research Triangle Park, NC 27709

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Greenville, NC 27834 or

GlaxoSmithKline

Research Triangle Park, NC 27709

LAMICTAL Orally Disintegrating Tablets are manufactured by

Eurand, Inc., Vandalia, OH 45377

December 2011

LMT:7MG

Principal Display Panel

NDC 0173-0633-02

LAM*ICTAL*®