**Table 3: Summary of AED Interactions With LAMICTAL**

| AED | AED Plasma Concentration With Adjunctive LAMICTAL* | Lamotrigine Plasma Concentration With Adjunctive AEDs† |
|---|---|---|
| Phenytoin (PHT) | ↔ | ↓ |
| Carbamazepine (CBZ) | ↔ | ↓ |
| CBZ epoxide‡ | ? | |
| Valproic acid (VPA) | ↓ | ↑ |
| VPA + PHT and/or CBZ | NE | ↔ |

* From adjunctive clinical trials and volunteer studies.

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

‡ Not administered, but an active metabolite of carbamazepine.

↔ = No significant effect.

? = Conflicting data.

NE = not evaluated.

***Specific Effects of Lamotrigine on the Pharmacokinetics of Other AED Products:***

***LAMICTAL Added to Phenytoin:*** LAMICTAL has no appreciable effect on steady-state phenytoin plasma concentration.

***LAMICTAL Added to Carbamazepine:*** LAMICTAL has no appreciable effect on steady-state carbamazepine plasma concentration. Limited clinical data suggest there is a higher incidence of dizziness, diplopia, ataxia, and blurred vision in patients receiving carbamazepine with LAMICTAL than in patients receiving other EIAEDs with LAMICTAL (see ADVERSE REACTIONS). 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 were seen to increase.

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

***Specific Effects of Other AED Products on the Pharmacokinetics of Lamotrigine: Phenytoin Added to LAMICTAL:*** The addition of phenytoin decreases lamotrigine steady-state concentrations by approximately 45% to 54% depending upon the total daily dose of phenytoin (i.e., from 100 to 400 mg).

***Carbamazepine Added to LAMICTAL:*** The addition of carbamazepine decreases lamotrigine steady-state concentrations by approximately 40%.

***Phenobarbital or Primidone Added to LAMICTAL:*** The addition of phenobarbital or

primidone decreases lamotrigine steady-state concentrations by approximately 40%.

***VPA Added to LAMICTAL:*** The addition of VPA increases lamotrigine steady-state concentrations in normal volunteers by slightly more than twofold.

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

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

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

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

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

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

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

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

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

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

**Pregnancy Exposure Registry:** To facilitate monitoring fetal outcomes of pregnant women exposed to lamotrigine, physicians are encouraged to register patients, **before fetal outcome (e.g., ultrasound, results of amniocentesis, birth, etc.) is known,** in the Antiepileptic Drug Pregnancy Registry by calling (888) 233-2334 (toll free).

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

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

**Pediatric Use:** In pediatric patients, LAMICTAL is only indicated as adjunctive therapy for the generalized seizures of Lennox-Gastaut syndrome. Safety and effectiveness for other uses in patients below the age of 16 years have not been established (see BOX WARNING).

**Geriatric Use:** Because few patients over the age of 65 (approximately 20) were exposed to LAMICTAL during its premarket evaluation, no specific statements about the safety or effectiveness of LAMICTAL in this age-group can be made.

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

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

higher incidence of rash, including serious rash, in patients receiving concomitant VPA than in patients not receiving VPA (see WARNINGS).

Approximately 11% of the 3378 adult patients who received LAMICTAL as adjunctive therapy in premarketing clinical trials discontinued treatment because of an adverse experience. The adverse events most commonly associated with discontinuation were: rash (3.0%), dizziness (2.8%), and headache (2.5%).

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

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

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

***Adjunctive Therapy in Pediatric Patients With Lennox-Gastaut Syndrome:*** The most commonly observed (≥ 5%) adverse experiences seen in association with the use of LAMICTAL as adjunctive treatment in pediatric patients with Lennox-Gastaut syndrome and not seen at an equivalent rate in the control group were pharyngitis, infection, rash, vomiting, bronchitis, accidental injury, constipation, and flu syndrome.

In 169 patients with Lennox-Gastaut syndrome (26 patients were between the ages of 16 and 25), 3.8% of patients on LAMICTAL and 7.8% of patients on placebo discontinued due to adverse experiences. The most commonly reported adverse experiences that led to discontinuation were rash for patients treated with LAMICTAL and deterioration of seizure control for patients treated with placebo.

Approximately 10% of the 1136 pediatric patients who received LAMICTAL as adjunctive therapy in premarketing clinical trials discontinued treatment because of an adverse experience. The adverse events most commonly associated with discontinuation were rash (3.9%), reaction aggravated (1.7%), and ataxia (0.9%).

**Incidence in Controlled Clinical Studies:** The prescriber should be aware that the figures in Tables 4, 5, 6, and 7 cannot be used to predict the frequency of adverse experiences in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An

inspection of these frequencies, however, does provide the prescriber with one basis to estimate the relative contribution of drug and nondrug factors to the adverse event incidences in the population studied.

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

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

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

| | | |
|---|---|---|
| Ataxia | 22 | 6 |
| Somnolence | 14 | 7 |
| Incoordination | 6 | 2 |
| Insomnia | 6 | 2 |
| Tremor | 4 | 1 |
| Depression | 4 | 3 |
| Anxiety | 4 | 3 |
| Convulsion | 3 | 1 |
| Irritability | 3 | 2 |
| Speech disorder | 3 | 0 |
| Concentration disturbance | 2 | 1 |
| Respiratory | | |
| Rhinitis | 14 | 9 |
| Pharyngitis | 10 | 9 |
| Cough increased | 8 | 6 |
| Skin and appendages | | |
| Rash | 10 | 5 |
| Pruritus | 3 | 2 |
| Special senses | | |
| Diplopia | 28 | 7 |
| Blurred vision | 16 | 5 |
| Vision abnormality | 3 | 1 |
| Urogenital | | |
| Female patients only | (n = 365) | (n = 207) |
| Dysmenorrhea | 7 | 6 |
| Vaginitis | 4 | 1 |
| Amenorrhea | 2 | 1 |

* Patients in these adjunctive studies were receiving one to three concomitant EIAEDs in addition to LAMICTAL or placebo. Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category.

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

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

**Table 5: Dose-Related Adverse Events From a Randomized, Placebo-Controlled Trial in Adults**

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

*Significantly greater than placebo group ($P<0.05$).

†Significantly greater than group receiving LAMICTAL 300 mg ($P<0.05$).

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

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

***Incidence in a Controlled Monotherapy Trial in Adults With Partial Seizures:*** Table 6 lists treatment-emergent signs and symptoms that occurred in at least 2% of patients with epilepsy treated with monotherapy with LAMICTAL in a double-blind trial following discontinuation of either concomitant carbamazepine or phenytoin not seen at an equivalent frequency in the control group.

**Table 6: Treatment-Emergent Adverse Event Incidence in Adults in a Controlled Monotherapy Trial* (Events in at least 2% of patients treated with LAMICTAL and numerically more frequent than in the valproate [VPA] group.)**

| Body System/ Adverse Experience† | Percent of Patients Receiving LAMICTAL Monotherapy‡ (n = 43) | Percent of Patients Receiving Low-Dose VPA§ Monotherapy (n = 44) |
|---|---|---|

| | | |
|---|---|---|
| Body as a whole | | |
| Pain | 5 | 0 |
| Infection | 5 | 2 |
| Chest pain | 5 | 2 |
| Asthenia | 2 | 0 |
| Fever | 2 | 0 |
| Digestive | | |
| Vomiting | 9 | 0 |
| Dyspepsia | 7 | 2 |
| Nausea | 7 | 2 |
| Anorexia | 2 | 0 |
| Dry mouth | 2 | 0 |
| Rectal hemorrhage | 2 | 0 |
| Peptic ulcer | 2 | 0 |
| Metabolic and nutritional | | |
| Weight decrease | 5 | 2 |
| Peripheral edema | 2 | 0 |
| Nervous | | |
| Coordination abnormality | 7 | 0 |
| Dizziness | 7 | 0 |
| Anxiety | 5 | 0 |
| Insomnia | 5 | 2 |
| Amnesia | 2 | 0 |
| Ataxia | 2 | 0 |
| Depression | 2 | 0 |
| Hypesthesia | 2 | 0 |
| Libido increase | 2 | 0 |
| Decreased reflexes | 2 | 0 |
| Increased reflexes | 2 | 0 |
| Nystagmus | 2 | 0 |
| Irritability | 2 | 0 |
| Suicidal ideation | 2 | 0 |
| Respiratory | | |
| Rhinitis | 7 | 2 |
| Epistaxis | 2 | 0 |
| Bronchitis | 2 | 0 |
| Dyspnea | 2 | 0 |
| Skin and appendages | | |
| Contact dermatitis | 2 | 0 |
| Dry skin | 2 | 0 |

| | | |
|---|---|---|
| Sweating | 2 | 0 |
| Special senses | | |
| Vision abnormality | 2 | 0 |
| Urogenital (female patients only) | (n = 21) | (n = 28) |
| Dysmenorrhea | 5 | 0 |

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

† Adverse experiences reported by at least 2% of patients are included.

‡ Up to 500 mg/day.

§ 1000 mg/day.

***Incidence in a Controlled Adjunctive Trial in Adult and Pediatric Patients With Lennox-Gastaut Syndrome:*** Table 7 lists adverse events that occurred in at least 2% of 79 adult and pediatric patients who received LAMICTAL up to 15 mg/kg per day or a maximum of 400 mg/kg per day. Reported adverse events were classified using COSTART terminology.

**Table 7: Treatment-Emergent Adverse Event Incidence in Placebo-Controlled Adjunctive Trial in Adult and Pediatric Patients With Lennox-Gastaut Syndrome (Events in at least 2% of patients treated with LAMICTAL and numerically more frequent than in the placebo group.)**

| Body System/ Adverse Experience | Percent of Patients Receiving LAMICTAL (n = 79) | Percent of Patients Receiving Placebo (n = 90) |
|---|---|---|
| Body as a whole | | |
| Infection | 13 | 8 |
| Accidental injury | 9 | 7 |
| Flu syndrome | 5 | 0 |
| Asthenia | 3 | 1 |
| Abdominal pain | 3 | 0 |
| Cardiovascular | | |
| Hemorrhage | 3 | 0 |
| Digestive | | |
| Vomiting | 9 | 7 |
| Constipation | 5 | 2 |
| Diarrhea | 4 | 2 |

| | | |
|---|---|---|
| Nausea | 4 | 1 |
| Anorexia | 3 | 1 |
| Nervous system | | |
| Ataxia | 4 | 1 |
| Convulsions | 4 | 1 |
| Tremor | 3 | 0 |
| Respiratory | | |
| Pharyngitis | 14 | 10 |
| Bronchitis | 9 | 7 |
| Pneumonia | 3 | 0 |
| Skin | | |
| Rash | 9 | 7 |
| Eczema | 4 | 0 |
| Urogenital | | |
| Urinary tract infection | 3 | 0 |
| Balanitis | 2 | 0 |
| Penis disorder | 2 | 0 |

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**Other Adverse Events Observed During All Clinical Trials For Adult and Pediatric Patients:** LAMICTAL has been administered to 3923 individuals for whom complete adverse event data was captured during all clinical trials, only some of which were placebo controlled. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. The frequencies presented represent the proportion of the 3923 individuals exposed to LAMICTAL who experienced an event of the type cited on at least one occasion while receiving LAMICTAL. All reported events are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* adverse events are defined as those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; *rare* adverse events are those occurring in fewer than 1/1000 patients.

***Body as a Whole: Frequent:*** Pain. ***Infrequent:*** Accidental injury, allergic reaction, back pain, chills, face edema, halitosis, infection, and malaise. ***Rare:*** Abdomen enlarged, abscess, photosensitivity, and suicide attempt.

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

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

***Digestive System: Infrequent:*** Dry mouth, dysphagia, gingivitis, glossitis, gum hyperplasia, increased appetite, increased salivation, liver function tests abnormal, mouth ulceration, stomatitis, thirst, and tooth disorder. ***Rare:*** Eructation, gastritis, gastrointestinal hemorrhage, gum hemorrhage, hematemesis, hemorrhagic colitis, hepatitis, melena, stomach ulcer, and tongue edema.

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

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

***Metabolic and Nutritional Disorders: Infrequent:*** Peripheral edema, weight gain, and weight loss. ***Rare:*** Alcohol intolerance, alkaline phosphatase increase, bilirubinemia, general edema, and hyperglycemia.

***Musculoskeletal System: Infrequent:*** Joint disorder, myasthenia, and twitching. ***Rare:*** Arthritis, bursitis, leg cramps, pathological fracture, and tendinous contracture.

***Nervous System: Frequent:*** Amnesia, confusion, hostility, memory decrease, nervousness, nystagmus, thinking abnormality, and vertigo. ***Infrequent:*** Abnormal dreams, abnormal gait,

agitation, akathisia, apathy, aphasia, CNS depression, depersonalization, dysarthria, dyskinesia, dysphoria, emotional lability, euphoria, faintness, grand mal convulsions, hallucinations, hyperkinesia, hypertonia, hypesthesia, libido increased, mind racing, muscle spasm, myoclonus, panic attack, paranoid reaction, personality disorder, psychosis, sleep disorder, and stupor. ***Rare:*** Cerebrovascular accident, cerebellar syndrome, cerebral sinus thrombosis, choreoathetosis, CNS stimulation, delirium, delusions, dystonia, hemiplegia, hyperalgesia, hyperesthesia, hypoesthesia, hypokinesia, hypomania, hypotonia, libido decreased, manic depression reaction, movement disorder, neuralgia, neurosis, paralysis, and suicidal ideation.

***Respiratory System: Infrequent:*** Dyspnea, epistaxis, and hyperventilation. ***Rare:*** Bronchospasm, hiccup, and sinusitis.

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

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

**Postmarketing and Other Experience:** In addition to the adverse experiences reported during clinical testing of LAMICTAL, the following adverse experiences have been reported in patients receiving marketed LAMICTAL in other countries and from worldwide noncontrolled investigational use. These adverse experiences have not been listed above, and data are insufficient to support an estimate of their incidence or to establish causation. The listing is alphabetized: Aplastic anemia, apnea, disseminated intravascular coagulation, esophagitis, hemolytic anemia, hypersensitivity reaction, multiorgan failure, neutropenia, pancreatitis, pancytopenia, and progressive immunosuppression.

**DRUG ABUSE AND DEPENDENCE:** The abuse and dependence potential of LAMICTAL have not been evaluated in human studies.

**OVERDOSAGE:**

**Human Overdose Experience:** Experience with single or daily doses ≥700 mg is limited. During the clinical development of LAMICTAL, the highest known overdoses were in two women who each ingested doses ≥4000 mg. The plasma concentration of lamotrigine in one woman was 52 mcg/mL 4 hours after the ingestion (a value more than 10 times greater than that seen in clinical trials). She became comatose and remained comatose for 8 to 12 hours; no electrocardiographic abnormalities were detected. The other patient had dizziness, headache, and somnolence. Both women recovered without sequelae.

Among patients ≤16 years of age, the two highest known single doses of LAMICTAL have been 3000 mg by a 14-year-old female and approximately 1000 mg by a 4-year-old male. The 14-year-old female was taking LAMICTAL; after the dose, she lost consciousness and was admitted to the

hospital for supportive therapy, where she recovered fully (time to recovery not reported). The 4-year-old male was drowsy and agitated when found, and progressed to coma. He was given supportive therapy, and his condition improved rapidly with full recovery in 3 days.

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

## DOSAGE AND ADMINISTRATION:

**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, e.g., carbamazepine, phenytoin, phenobarbital, etc.).

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

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

**General Dosing Considerations:** The risk of nonserious rash is increased when the recommended initial dose and/or the rate of dose escalation of LAMICTAL is exceeded. There are suggestions, yet to be proven, that the risk of severe, potentially life-threatening rash may be increased by 1) coadministration of LAMICTAL with 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 (see BOX WARNING). Therefore, it is important that the dosing recommendations be followed closely.

**Adjunctive Therapy With LAMICTAL:** This section provides specific dosing recommendations for patients 2 to 12 years of age and patients greater than 12 years of age. Within each of these age-groups, specific dosing recommendations are provided depending upon whether or not the patient is receiving VPA (Tables 8 and 9 for patients 2 to 12 years of age, Tables 10 and 11 for patients greater than 12 years of age). In addition, the section provides a discussion of dosing for

those patients receiving concomitant AEDs that have not been systematically evaluated in combination with LAMICTAL.

For dosing guidelines for LAMICTAL below, enzyme-inducing antiepileptic drugs (EIAEDs) include phenytoin, carbamazepine, phenobarbital, and primidone.

***Patients 2 to 12 Years of Age:*** Recommended dosing guidelines for LAMICTAL added to an antiepileptic drug (AED) regimen containing VPA are summarized in Table 8. Recommended dosing guidelines for LAMICTAL added to EIAEDs are summarized in Table 9. Note that the starting doses and dose escalations listed below are different than those used in clinical trials; however, the maintenance doses are the same as in clinical trials. Smaller starting doses and slower dose escalations than those used in clinical trials are recommended because of the suggestions that the risk of rash may be decreased by smaller starting doses and slower dose escalations. Therefore, maintenance doses will take longer to reach in clinical practice than in clinical trials. It may take several weeks to months to achieve an individualized maintenance dose. It is likely that patients aged 2 to 6 years will require a maintenance dose at the higher end of the maintenance dose range.

**The smallest available strength of LAMICTAL Chewable Dispersible Tablets is 5 mg, and only whole tablets should be administered. If the calculated dose cannot be achieved using whole tablets, the dose should be rounded down to the nearest whole tablet.**

**Pediatric patients who weigh less than 17 kg (37 lb) should not receive LAMICTAL because therapy cannot be initiated using the dosing guidelines (see Table 8 and Table 9) and the currently available tablet strengths (see WARNINGS).**

**Table 8: LAMICTAL Added to an AED Regimen Containing VPA in Patients 2 to 12 Years of Age**

| | |
|---|---|
| Weeks 1 and 2 | 0.15 mg/kg/day in one or two divided doses, rounded down to the nearest 5 mg.<br>If the initial calculated daily dose of LAMICTAL is 2.5 to 5 mg, then 5 mg of LAMICTAL should be taken on alternate days for the first 2 weeks |
| Weeks 3 and 4 | 0.3 mg/kg/day in one or two divided doses, rounded down to the nearest 5 mg. |
| Usual maintenance dose: 1 to 5 mg/kg/day (maximum 200 mg/day in one or two divided doses). To achieve the usual maintenance dose, subsequent doses should be increased every 1 to 2 weeks as follows: calculate 0.3 mg/kg/day, round this amount down to the nearest 5 mg, and add this amount to the previously administered daily dose. | |

838 **Table 9: LAMICTAL Added to EIAEDs (Without VPA) in Patients 2 to 12 Years of Age**
839

| | |
|---|---|
| Weeks 1 and 2 | 0.6 mg/kg/day in two divided doses, rounded down to the nearest 5 mg. |
| Weeks 3 and 4 | 1.2 mg/kg/day in two divided doses, rounded down to the nearest 5 mg. |
| Usual maintenance dose: 5 to 15 mg/kg/day (maximum 400 mg/day in two divided doses). To achieve the usual maintenance dose, subsequent doses should be increased every 1 to 2 weeks as follows: calculate 1.2 mg/kg/day, round this amount down to the nearest 5 mg, and add this amount to the previously administered daily dose. | |

840

841 ***Patients Over 12 Years of Age:*** Recommended dosing guidelines for LAMICTAL added to VPA
842 are summarized in Table 10. Recommended dosing guidelines for LAMICTAL added to EIAEDs are
843 summarized in Table 11.

844

845 **Table 10: LAMICTAL Added to an AED Regimen Containing VPA**
846 **in Patients Over 12 Years of Age**
847

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

848

849 **Table 11: LAMICTAL Added to EIAEDs (Without VPA)**
850 **in Patients Over 12 Years of Age**
851

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

852

853 **Conversion From a Single EIAED to Monotherapy with LAMICTAL in Patients ≥16 Years of**
854 **Age:** The goal of the transition regimen is to effect the conversion to LAMICTAL monotherapy under
855 conditions that ensure adequate seizure control while mitigating the risk of serious rash associated
856 with the rapid titration of LAMICTAL.
857 The conversion regimen involves two steps. In the first, LAMICTAL is titrated to the targeted dose
858 while maintaining the dose of the EIAED at a fixed level; in the second step, the EIAED is gradually
859 withdrawn over a period of 4 weeks.
860 The recommended maintenance dose of LAMICTAL as monotherapy is 500 mg/day given in two
861 divided doses.

LAMICTAL should be added to an EIAED to achieve a dose of 500 mg/day according to the guidelines in Table 11 above. The regimen for the withdrawal of the concomitant EIAED is based on experience gained in the controlled monotherapy clinical trial. In that trial, the concomitant EIAED was withdrawn by 20% decrements each week over a 4-week period.

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

**Usual Maintenance Dose:** The usual maintenance doses identified in the tables above are derived from dosing regimens employed in the placebo-controlled adjunctive studies in which the efficacy of LAMICTAL was established. In patients receiving multidrug regimens employing EIAEDs **without VPA**, maintenance doses of adjunctive LAMICTAL as high as 700 mg/day have been used. In patients receiving **VPA alone**, maintenance doses of adjunctive LAMICTAL as high as 200 mg/day have been used. The advantage of using doses above those recommended in the tables above has not been established in controlled trials.

**LAMICTAL Added to AEDs Other Than EIAEDs and VPA:** The effect of AEDs other than EIAEDs and VPA on the metabolism of LAMICTAL cannot be predicted. Therefore, no specific dosing guidelines can be provided in that situation. Conservative starting doses and dose escalations (as with concomitant VPA) would be prudent; maintenance dosing would be expected to fall between the maintenance dose with VPA and the maintenance dose without VPA, but with an EIAED.

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

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

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

*Discontinuing an EIAED should prolong the half-life of lamotrigine; discontinuing VPA should shorten the half-life of lamotrigine.*

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

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

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

**HOW SUPPLIED:** LAMICTAL Tablets, 25 mg, white, scored, shield-shaped tablets engraved with "LAMICTAL" and "25", bottles of 25 (NDC 0173-0633-25) and 100 (NDC 0173-0633-02).

**Store at 15° to 25°C (59° to 77°F) in a dry place.**

LAMICTAL Tablets, 100 mg, peach, scored, shield-shaped tablets engraved with "LAMICTAL" and "100", bottle of 100 (NDC 0173-0642-55).

LAMICTAL Tablets, 150 mg, cream, scored, shield-shaped tablets engraved with "LAMICTAL" and "150", bottle of 60 (NDC 0173-0643-60).

LAMICTAL Tablets, 200 mg, blue, scored, shield-shaped tablets engraved with "LAMICTAL" and "200", bottle of 60 (NDC 0173-0644-60).

**Store at 15° to 25°C (59° to 77°F) in a dry place and protect from light.**

LAMICTAL Chewable Dispersible Tablets, 5 mg, white, caplet-shaped tablets engraved with "GX CL2", bottle of 100 (NDC 0173-0526-00).

LAMICTAL Chewable Dispersible Tablets, 25 mg, white, super elliptical-shaped tablets engraved with "GX CL5", bottle of 100 (NDC 0173-0527-00).

**Store at controlled room temperature, 20° to 25°C (68° to 77°F) (see USP) in a dry place.**

**PATIENT INFORMATION:** The following wording is contained in a separate leaflet provided for patients.

**Information for the Patient**

**LAMICTAL® (lamotrigine) Tablets**

|  |  |  |  |
|---|---|---|---|
| **25 mg, white** | **100 mg, peach** | **150 mg, cream** | **200 mg, blue** |

**LAMICTAL® (lamotrigine) Chewable Dispersible Tablets**

|  |  |
|---|---|
| **5 mg, white** | **25 mg, white** |

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

**Information About Your Medicine:**

The name of your medicine is LAMICTAL (lamotrigine). The decision to use LAMICTAL is one that you and your doctor should make together.

***1. The Purpose of Your Medicine:***

Lamotrigine is intended to be used either alone or in combination with other medicines to treat seizures in people age 16 years or older and/or only those patients below the age of 16 years who have seizures associated with the Lennox-Gastaut syndrome. When taking lamotrigine, it is important to follow your doctor's instructions.

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

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

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

- Most people who take LAMICTAL tolerate it well. The most common side effects with LAMICTAL are dizziness, headache, blurred or double vision, lack of coordination, sleepiness, nausea, vomiting, and rash.
- Although most patients who develop rash while receiving LAMICTAL have mild to moderate symptoms, some individuals may develop a serious skin reaction that requires hospitalization. Rarely, deaths have been reported. These serious skin reactions are most likely to happen within the first 8 weeks of treatment with LAMICTAL. Serious skin reactions occur more often in children than in adults.
- Rashes may be more likely to occur if you: 1) take LAMICTAL in combination with valproic acid (DEPAKENE® or DEPAKOTE®), 2) take a higher starting dose of LAMICTAL than your doctor prescribed, or 3) increase your dose of LAMICTAL faster than prescribed.
- It is not possible to predict whether a mild rash will develop into a more serious reaction. **Therefore, if you experience a skin rash, hives, fever, swollen lymph glands, painful sores in the mouth or around the eyes, or swelling of lips or tongue, tell a doctor immediately, since these symptoms may be the first signs of a serious reaction. A doctor should evaluate your condition and decide if you should continue taking LAMICTAL.**

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

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

***5. How to Use LAMICTAL:***

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

- Tell your doctor if your seizures get worse or if you have any new types of seizures.
- Always tell your doctor and pharmacist if you are taking or plan to take any other prescription or over-the-counter medicines.

***6. How to Take LAMICTAL:***

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

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

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***7. Storing Your Medicine:***

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

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

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

**GlaxoWellcome**
Glaxo Wellcome Inc.
Research Triangle Park, NC 27709



US Patent No. 4,602,017



October 1998 RL-

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

**Information for the Patient**

**LAMICTAL® (lamotrigine) Tablets**
**LAMICTAL® (lamotrigine) Chewable Dispersible Tablets**

**LAMICTAL® (lamotrigine) Tablets**

| | | | |
|---|---|---|---|
|  |  |  |  |
| 25 mg, white | 100 mg, peach | 150 mg, cream | 200 mg, blue |

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| | |
|---|---|
|  |  |
| 5 mg, white | 25 mg, white |

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- Do NOT stop taking LAMICTAL or any of your other seizure medicines unless instructed by your doctor.
- Use caution before driving a car or operating complex, hazardous machinery until you know if LAMICTAL affects your ability to perform these tasks.
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**GlaxoWellcome**
Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

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US Patent No. 4,602,017



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