

Propranolol Shows Early Promise for PTSD

BY KATE JOHNSON

FROM THE ANNUAL MEETING OF THE INTERNATIONAL SOCIETY FOR TRAUMATIC STRESS STUDIES

MONTREAL – Treatment of posttraumatic stress disorder with the beta-blocker propranolol might interrupt memory reconsolidation by inhibiting protein synthesis in the brain, reported researchers at the International Society for Trau-

matic Stress Studies.

“It does not erase memories; this is a misnomer,” clarified Alain Brunet, Ph.D., of the department of psychiatry at McGill University and a researcher at the Douglas Mental Health Institute, both in Montreal.

Dr. Brunet presented several studies conducted by his group that suggest this pharmacologic interruption of memory might dampen emotional response to

the information, presenting a promising treatment opportunity for posttraumatic stress disorder (PTSD).

Current treatment for PTSD is centered on psychotherapy that focuses on exposure to the traumatic memory and learning new responses to it, Dr. Brunet said. But a recent analysis found that only about one-third of patients treated this way experience a lasting, clinically meaningful improvement, he said.

Propranolol treatment takes a different approach. It is based on the notion that memories, once they are consolidated, can be retrieved, and they exist in a labile state during which they are susceptible to modification until they are reconsolidated. During the labile window of opportunity, which is believed to be several hours, administration of propranolol can strip the memory of its emotional meaning, making it less stressful, he said.

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BRIEF SUMMARY

The following is a brief summary only; see full prescribing information for complete product information.

WARNING: SERIOUS SKIN RASHES

LAMICTAL® can cause serious rashes requiring hospitalization and discontinuation of treatment. The incidence of these rashes, which have included Stevens-Johnson syndrome, is approximately 0.8% (8 per 1,000) in pediatric patients (2 to 16 years of age) receiving LAMICTAL as adjunctive therapy for epilepsy and 0.3% (3 per 1,000) in adults on adjunctive therapy for epilepsy. In clinical trials of bipolar and other mood disorders, the rate of serious rash was 0.08% (0.8 per 1,000) in adult patients receiving LAMICTAL as initial monotherapy and 0.13% (1.3 per 1,000) in adult patients receiving LAMICTAL as adjunctive therapy. In a prospectively followed cohort of 1,983 pediatric patients (2 to 16 years of age) with epilepsy taking adjunctive LAMICTAL, there was 1 rash-related death. In worldwide postmarketing experience, rare cases of toxic epidermal necrolysis and/or rash-related death have been reported in adult and pediatric patients, but their numbers are too few to permit a precise estimate of the rate.

Other than age, there are as yet no factors identified that are known to predict the risk of occurrence or the severity of rash caused by LAMICTAL. There are suggestions, yet to be proven, that the risk of rash may also be increased by (1) coadministration of LAMICTAL with valproate (includes valproic acid and divalproex sodium), (2) exceeding the recommended initial dose of LAMICTAL, or (3) exceeding the recommended dose escalation for LAMICTAL. However, cases have occurred in the absence of these factors.

Nearly all cases of life-threatening rashes caused by LAMICTAL have occurred within 2 to 8 weeks of treatment initiation. However, isolated cases have occurred after prolonged treatment (e.g., 6 months). Accordingly, duration of therapy cannot be relied upon as means to predict the potential risk heralded by the first appearance of a rash.

Although benign rashes are also caused by LAMICTAL, it is not possible to predict reliably which rashes will prove to be serious or life-threatening. Accordingly, LAMICTAL should ordinarily be discontinued at the first sign of rash, unless the rash is clearly not drug-related. Discontinuation of treatment may not prevent a rash from becoming life-threatening or permanently disabling or disfiguring [see Warnings and Precautions (5.1)].

4 CONTRAINDICATIONS

LAMICTAL is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients [see Boxed Warning].

5 WARNINGS AND PRECAUTIONS

5.1 Serious Skin Rashes [see Boxed Warning]:

Pediatric Population: The incidence of serious rash associated with hospitalization and discontinuation of LAMICTAL in a prospectively followed cohort of pediatric patients (2 to 16 years of age) with epilepsy receiving adjunctive therapy was approximately 0.8% (16 of 1,983). When 14 of these cases were reviewed by 3 expert dermatologists, there was considerable disagreement as to their proper classification. To illustrate, one dermatologist considered none of the cases to be Stevens-Johnson syndrome; another assigned 7 of the 14 to this diagnosis. There was 1 rash-related death in this 1,983-patient cohort. Additionally, there have been rare cases of toxic epidermal necrolysis with and without permanent sequelae and/or death in US and foreign postmarketing experience. There is evidence that the inclusion of valproate in a multidrug regimen increases the risk of serious, potentially life-threatening rash in pediatric patients. In pediatric patients who used valproate concomitantly, 1.2% (6 of 482) experienced a serious rash compared with 0.6% (6 of 952) patients not taking valproate.

Adult Population: Serious rash associated with hospitalization and discontinuation of LAMICTAL occurred in 0.3% (11 of 3,348) of adult patients who received LAMICTAL in premarketing clinical trials of epilepsy. In the bipolar and other mood disorders clinical trials, the rate of serious rash was 0.08% (1 of 1,233) of adult patients who received LAMICTAL as initial monotherapy and 0.13% (2 of 1,538) of adult patients who received LAMICTAL as adjunctive therapy. No fatalities occurred among these individuals. However, in worldwide postmarketing experience, rare cases of rash-related death have been reported, but their numbers are too few to permit a precise estimate of the rate. Among the rashes leading to hospitalization were Stevens-Johnson syndrome, toxic epidermal necrolysis, angioedema, and a rash associated with a variable number of the following systemic manifestations: fever, lymphadenopathy, facial swelling, and hematologic and hepatic abnormalities. There is evidence that the inclusion of valproate in a multidrug regimen increases the risk of serious, potentially life-threatening rash in adults. Specifically, of 584 patients administered LAMICTAL with valproate in epilepsy clinical trials, 6 (1%) were hospitalized in association with rash; in contrast, 4 (0.16%) of 2,398 clinical trial patients and volunteers administered LAMICTAL in the absence of valproate were hospitalized.

Patients With History of Allergy or Rash to Other AEDs: The risk of nonserious rash may be increased when the recommended initial dose and/or the rate of dose escalation of LAMICTAL is exceeded and in patients with a history of allergy or rash to other AEDs.

5.2 Hypersensitivity Reactions: Hypersensitivity reactions, some fatal or life-threatening, have also occurred. Some of these reactions have included clinical features of multiorgan failure/dysfunction, including hepatic abnormalities and evidence of disseminated intravascular coagulation. It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even though a rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. LAMICTAL should be discontinued if an alternative etiology for the signs or symptoms cannot be established. Prior to initiation of treatment with LAMICTAL, the patient should be instructed that a rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy) may herald a serious medical event and that the patient should report any such occurrence to a physician immediately.

5.3 Acute Multiorgan Failure: Multiorgan failure, which in some cases has been fatal or irreversible, has been observed in patients receiving LAMICTAL. Fatalities associated with multiorgan failure and various degrees of hepatic failure have been reported in 2 of 3,796 adult patients and 4 of 2,435 pediatric patients who received LAMICTAL in epilepsy clinical trials. No such fatalities have been reported in bipolar patients in clinical trials. Rare fatalities from multiorgan failure have also been reported in compassionate plea and postmarketing use. The majority of these deaths occurred in association with other serious medical events, including status epilepticus and overwhelming sepsis, and hantavirus, making it difficult to identify the initial cause. Additionally, 3 patients (a 45-year-old woman, a 3.5-year-old boy, and an 11-year-old girl) developed multiorgan dysfunction and disseminated intravascular coagulation 9 to 14 days after LAMICTAL was added to their AED regimens. Rash and elevated transaminases were also present in all patients and rhabdomyolysis was noted in 2 patients. Both pediatric patients were receiving concomitant therapy with valproate, while the adult patient was being treated with carbamazepine and clonazepam. All patients subsequently recovered with supportive care after treatment with LAMICTAL was discontinued.

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

5.5 Suicidal Behavior and Ideation: Antiepileptic drugs (AEDs), including LAMICTAL, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI: 1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately 1 case of suicidal thinking or behavior for every 530 patients treated. There were 4 suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number of events is too small to allow any conclusion about drug effect on suicide. The increased risk of suicidal thoughts or behavior with AEDs was observed as early as 1 week after starting treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed. The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding

of increased risk with AEDs of varying mechanism of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5 to 100 years) in the clinical trials analyzed. Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1. Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

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

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications. Anyone considering prescribing LAMICTAL or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated. Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

5.6 Use in Patients With Bipolar Disorder: Acute Treatment of Mood Episodes: Safety and effectiveness of LAMICTAL in the acute treatment of mood episodes have not been established. **Children and Adolescents (less than 18 years of age):** Safety and effectiveness of LAMICTAL in patients below the age of 18 years with mood disorders have not been established [see Suicidal Behavior and Ideation (5.5)]. **Clinical Worsening and Suicide Risk Associated With Bipolar Disorder:** Patients with bipolar disorder may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviors (suicidality) whether or not they are taking medications for bipolar disorder. Patients should be closely monitored for clinical worsening (including development of new symptoms) and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes. In addition, patients with a history of suicidal behavior or thoughts, those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults are at an increased risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment [see Suicidal Behavior and Ideation (5.5)]. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who experience clinical worsening (including development of new symptoms) and/or the emergence of suicidal ideation/behavior especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Prescriptions for LAMICTAL should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose. Overdoses have been reported for LAMICTAL, some of which have been fatal [see Overdose (10.1)].

5.7 Potential Medication Errors: Medication errors involving LAMICTAL have occurred. In particular, the name 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 the 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.

5.8 Concomitant Use With Oral Contraceptives: Some estrogen containing oral contraceptives have been shown to decrease serum concentrations of lamotrigine [see Clinical Pharmacology (12.3) of full prescribing information]. **Dosage adjustments will be necessary in most patients who start or stop estrogen-containing oral contraceptives while taking LAMICTAL [see Dosage and Administration (2.1) of full prescribing information].** During the week of inactive hormone preparation ("pill-free" week) of oral contraceptive therapy, plasma lamotrigine levels are expected to rise, as much as doubling at the end of the week. Adverse reactions consistent with elevated levels of lamotrigine, such as dizziness, ataxia, and diplopia, could occur.

5.9 Withdrawal Seizures: As with other AEDs, LAMICTAL should not be abruptly discontinued. In patients with epilepsy there is a possibility of increasing seizure frequency. In clinical trials in patients with Bipolar Disorder, 2 patients experienced seizures shortly after abrupt withdrawal of LAMICTAL. However, there were confounding factors that may have contributed to the occurrence of seizures in these bipolar patients. Unless safety concerns require a more rapid withdrawal, the dose of LAMICTAL should be tapered over a period of at least 2 weeks (approximately 50% reduction per week) [see Dosage and Administration (2.1) of full prescribing information].

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

5.11 Sudden Unexplained Death in Epilepsy (SUDEP): During the premarketing development of LAMICTAL, 20 sudden and unexplained deaths were recorded among a cohort of 4,700 patients with epilepsy (5,747 patient-years of exposure). Some of these could represent seizure-related deaths in which the seizure was not observed, e.g., at night. This represents an incidence of 0.0035 deaths per patient-year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving LAMICTAL (ranging from 0.0005 for the general population of patients with epilepsy, to 0.004 for a recently studied clinical trial population similar to that in the clinical development program for LAMICTAL, to 0.005 for patients with refractory epilepsy). Consequently, whether these figures are reassuring or suggest concern depends on the comparability of the populations reported upon to the cohort receiving LAMICTAL and the accuracy of the estimates provided. Probably most reassuring is the similarity of estimated SUDEP rates in patients receiving LAMICTAL and those receiving other AEDs, chemically unrelated to each other, that underwent clinical testing in similar populations. Importantly, that drug is chemically unrelated to LAMICTAL. This evidence suggests, although it certainly does not prove, that the high SUDEP rates reflect population rates, not a drug effect.

5.12 Addition of LAMICTAL to a Multidrug Regimen That Includes Valproate: Because valproate reduces the clearance of lamotrigine, the dosage of lamotrigine in the presence of valproate is less than half of that required in its absence.

5.13 Binding in the Eye and Other Melanin-Containing Tissues: Because lamotrigine binds to melanin, it could accumulate in melanin-rich tissues over time. This raises the possibility that lamotrigine may cause toxicity in these tissues after extended use. Although ophthalmological testing was performed in one controlled clinical trial, the testing was inadequate to exclude subtle effects or injury occurring after long-term exposure. Moreover, the capacity of available tests to detect potentially adverse consequences, if any, of lamotrigine's binding to melanin is unknown [see Clinical Pharmacology (12.2) of full prescribing information]. Accordingly, although there are no specific recommendations for periodic ophthalmological monitoring, prescribers should be aware of the possibility of long-term ophthalmologic effects.

5.14 Laboratory Tests: The value of monitoring plasma concentrations of lamotrigine in patients treated with LAMICTAL has not been established. Because of the possible pharmacokinetic interactions between lamotrigine and other drugs including AEDs [see Table 15 under Pharmacokinetics (12.3) in the full prescribing information], monitoring of the plasma levels of lamotrigine and concomitant drugs may be indicated, particularly during dosage adjustments. In general, clinical judgment should be exercised regarding monitoring of plasma levels of lamotrigine and other drugs and whether or not dosage adjustments are necessary.

Major Finding: Propranolol administered at traumatic memory recall appears to block reconsolidation of the memory.

Data Source: A randomized, controlled trial of 19 patients and two open-label studies totaling 42 patients, by the same group, showed a reduction in memory-induced signs and symptoms of traumatic stress.

Disclosures: Dr. Brunet had no disclosures to report.

In a randomized, controlled trial involving 19 chronic PTSD patients with an average symptom of duration 10 years (J. Psychiatr. Res. 2008;42:503-6),

Dr. Brunet and his colleagues asked the patients to recall their memory by writing a trauma script and outlining the details of their traumatic experience and the emotions they felt. Nine patients were then given a two-dose regimen of fast-acting propranolol (40 mg) immediately after memory recall, followed by an extended-release propranolol dose (60 mg) 75 minutes lat-

er, and the other 10 patients received placebo. One week later, after reviewing their trauma script, patients' physiologic responses to the memories were compared, using heart rate, skin conductivity, and corrugator electromyography (EMG) measurements.

Dr. Brunet reported significant differences between the placebo and treatment groups on heart rate and skin conductivity tests but not on EMG. There was a trend toward decreased symptoms, measured on the self-report Impact of Event Scale-Revised (IES-R).

The field of memory reconsolidation

blockade is young when it comes to human studies, but there is substantial animal research to support it, commented Dr. Charles Marmar, professor and chair in the department of psychiatry at New York University Medical Center, who chaired a panel discussion after the session.

"The notion of building a pipeline from basic science, to translational studies in humans, to new treatments is very, very important in psychiatry," he said in an interview. "This work is pioneering. We should have some patience about this and appreciate that this is a new paradigm in mental health research." ■

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6 ADVERSE REACTIONS

The following adverse reactions are described in more detail in the *Warnings and Precautions* section of the label: Serious skin rashes [see *Warnings and Precautions* (5.1)], Hypersensitivity reactions [see *Warnings and Precautions* (5.2)], Acute multiorgan failure [see *Warnings and Precautions* (5.3)], Blood dyscrasias [see *Warnings and Precautions* (5.4)], Suicidal behavior and ideation [see *Warnings and Precautions* (5.5)], Withdrawal seizures [see *Warnings and Precautions* (5.9)], Status epilepticus [see *Warnings and Precautions* (5.10)], Sudden unexplained death in epilepsy [see *Warnings and Precautions* (5.11)].

6.1 Clinical Trials: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. LAMICTAL has been evaluated for safety in patients with epilepsy and in patients with Bipolar I Disorder. Adverse reactions reported for each of these patient populations are provided below. Excluded are adverse reactions considered too general to be informative and those not reasonably attributable to the use of the drug.

Epilepsy: Most Common Adverse Reactions in All Clinical Studies: Adjunctive Therapy in Adults With Epilepsy: The most commonly observed (≥5% for LAMICTAL and more common on drug than placebo) adverse reactions seen in association with LAMICTAL during adjunctive therapy in adults and not seen at an equivalent frequency among placebo-treated patients were: dizziness, ataxia, somnolence, headache, diplopia, blurred vision, nausea, vomiting, and rash. Dizziness, diplopia, ataxia, blurred vision, nausea, and vomiting were dose-related. Dizziness, diplopia, ataxia, and blurred vision occurred more commonly in patients receiving carbamazepine with LAMICTAL than in patients receiving other AEDs with LAMICTAL. Clinical data suggest a higher incidence of rash, including serious rash, in patients receiving concomitant valproate than in patients not receiving valproate [see *Warnings and Precautions* (5.1)]. Approximately 11% of the 3,378 adult patients who received LAMICTAL as adjunctive therapy in premarketing clinical trials discontinued treatment because of an adverse reaction. The adverse reactions most commonly associated with discontinuation were rash (3.0%), dizziness (2.8%), and headache (2.5%). In a dose-response study in adults, the rate of discontinuation of LAMICTAL for dizziness, ataxia, diplopia, blurred vision, nausea, and vomiting was dose-related.

Monotherapy in Adults With Epilepsy: The most commonly observed (≥5% for LAMICTAL and more common on drug than placebo) adverse reactions 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% for LAMICTAL and more common on drug than placebo) adverse reactions 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 reaction. The adverse reactions most commonly associated with discontinuation were rash (4.5%), headache (3.1%), and asthenia (2.4%).

Adjunctive Therapy in Pediatric Patients With Epilepsy: The most commonly observed (≥5% for LAMICTAL and more common on drug than placebo) adverse reactions seen in association with the use of LAMICTAL as adjunctive treatment in pediatric patients 2 to 16 years of age and not seen at an equivalent rate in the control group were infection, vomiting, rash, fever, somnolence, accidental injury, dizziness, diarrhea, abdominal pain, nausea, ataxia, tremor, asthenia, bronchitis, flu syndrome, and diplopia. In 339 patients 2 to 16 years of age with partial seizures or generalized seizures of Lennox-Gastaut syndrome, 4.2% of patients on LAMICTAL and 2.9% of patients on placebo discontinued due to adverse reactions. The most commonly reported adverse reaction that led to discontinuation of LAMICTAL was rash. Approximately 11.5% of the 1,081 pediatric patients 2 to 16 years of age who received LAMICTAL as adjunctive therapy in premarketing clinical trials discontinued treatment because of an adverse reaction. The adverse reactions most commonly associated with discontinuation were rash (4.4%), reaction aggravated (1.7%), and ataxia (0.6%).

Controlled Adjunctive Clinical Studies in Adults With Epilepsy: Listed below are treatment-emergent adverse reactions 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 reactions were usually mild to moderate in intensity. LAMICTAL was administered as adjunctive therapy to 711 patients; 419 patients received adjunctive placebo. Patients in these adjunctive studies were receiving 1 to 3 of the following concomitant AEDs (carbamazepine, phenytoin, phenobarbital, or primidone) in addition to LAMICTAL or placebo. Patients may have reported multiple adverse reactions during the study or at discontinuation; thus, patients may be included in more than one category.

Treatment-Emergent Adverse Reaction Incidence in Placebo-Controlled Adjunctive Trials in Adult Patients With Epilepsy (Adverse events in at least 2% of patients treated with LAMICTAL and numerically more frequent than in the placebo group are listed by body system with the incidence for LAMICTAL followed by placebo): **Body as a whole:** Headache (29.1%), 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%), 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).

Dose-Related Adverse Reactions From a Randomized, Placebo-Controlled Adjunctive Trial in Adults With Epilepsy: In a randomized, parallel study comparing placebo (n = 73) and 300 (n = 71) and 500 mg/day (n = 72) of LAMICTAL, some of the more common drug-related adverse reactions were dose-related. The following adverse reactions are listed by incidence in placebo first, LAMICTAL 300 mg dose second, and LAMICTAL 500 mg dose third: 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). The overall adverse reaction 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 reaction reports by race. Generally, females receiving either LAMICTAL as adjunctive therapy or placebo were more likely to report adverse reactions than males. The only adverse reaction 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 reactions.

Controlled Monotherapy Trial in Adults With Partial Seizures: Listed below are treatment-emergent adverse reactions that occurred in at least 5% of patients with epilepsy treated with monotherapy with LAMICTAL in a double-blind trial following discontinuation of either concomitant carbamazepine or phenytoin not seen at an equivalent frequency in the control group. Forty-three patients received monotherapy with LAMICTAL up to 500 mg/day; 44 received low-dose valproate monotherapy at 1,000 mg/day. Patients in these studies were converted to LAMICTAL or valproate monotherapy from adjunctive therapy with carbamazepine or phenytoin. Patients may have reported multiple adverse experiences during the study; thus, patients may be included in more than one category.

Treatment-Emergent Adverse Reaction Incidence in Adults With Partial Seizures in a Controlled Monotherapy Trial (Adverse reactions in at least 5% of patients treated with LAMICTAL and numerically more frequent than in the valproate group are listed by body system with the incidence for LAMICTAL followed by valproate): **Body as a whole:** Pain (5.0%), infection (5.2%), chest pain (5.2); **Digestive:** Vomiting (9.0%), dyspepsia (7.2%), nausea (7.2); **Metabolic and nutritional:** Weight decrease (5.2); **Nervous:** Coordination abnormality (7.0%), dizziness (7.0%), anxiety (5.0%), insomnia (5.2); **Respiratory:** Rhinitis (7.2); **Urogenital (female patients only (n=21), (n=28):** Dysmenorrhea (5.0).

Adverse reactions that occurred with a frequency of less than 5% and greater than 2% of patients receiving LAMICTAL and numerically more frequent than placebo were: **Body as a Whole:** Asthenia, fever. **Digestive:** Anorexia, dry mouth,

rectal hemorrhage, peptic ulcer. **Metabolic and Nutritional:** Peripheral edema. **Nervous System:** Amnesia, ataxia, depression, hypesthesia, libido increase, decreased reflexes, increased reflexes, nystagmus, irritability, suicidal ideation. **Respiratory:** Epistaxis, bronchitis, dyspnea. **Skin and Appendages:** Contact dermatitis, dry skin, sweating. **Special Senses:** Vision abnormality. *Incidence in Controlled Adjunctive Trials in Pediatric Patients With Epilepsy:* Listed below are adverse reactions that occurred in at least 2% of 339 pediatric patients with partial seizures or generalized seizures of Lennox-Gastaut syndrome, who received LAMICTAL up to 15 mg/kg/day or a maximum of 750 mg/day. Reported adverse reactions were classified using COSTART terminology. LAMICTAL was administered as adjunctive therapy to 168 patients; 171 patients received adjunctive placebo.

Treatment-Emergent Adverse Reaction Incidence in Placebo-Controlled Adjunctive Trials in Pediatric Patients With Epilepsy (Adverse reactions in at least 2% of patients treated with LAMICTAL and numerically more frequent than in the placebo group are listed by body system with the incidence for LAMICTAL followed by placebo): **Body as a whole:** Infection (20.17%), fever (15.14%), accidental injury (14.12%), abdominal pain (10.5%), asthenia (8.4%), flu syndrome (7.6%), pain (5.4%), facial edema (2.1%), photosensitivity (2.0); **Cardiovascular:** Hemorrhage (2.1); **Digestive:** Vomiting (20.16%), diarrhea (11.9%), nausea (10.2%), constipation (4.2%), dyspepsia (2.1); **Hemic and lymphatic:** Lymphadenopathy (2.1); **Metabolic and nutritional:** Edema (2.0) **Nervous system:** Somnolence (17.15%), dizziness (14.4%), ataxia (11.3%), tremor (10.1%), emotional lability (4.2%), gait abnormality (4.2%), thinking abnormality (3.2%), convulsions (2.1), nervousness (2.1), vertigo (2.1); **Respiratory:** Pharyngitis (14.11%), bronchitis (7.5%), increased cough (7.6%), sinusitis (2.1), bronchospasm (2.1); **Skin:** Rash (14.12%), eczema (2.1), pruritus (2.1); **Special senses:** Diplopia (5.1%), blurred vision (4.1%), visual abnormality (2.0); **Urogenital:** (male and female patients) Urinary tract infection (3.0).

Bipolar Disorder: The most commonly observed (≥5%) treatment-emergent adverse reactions seen in association with the use of LAMICTAL as monotherapy (100 to 400 mg/day) in adult patients (≥18 years of age) with Bipolar Disorder in the 2 double-blind, placebo-controlled trials of 18 months' duration, and numerically more frequent than in placebo-treated patients are: **Treatment-Emergent Adverse Reaction Incidence in 2 Placebo-Controlled Trials in Adults With Bipolar I Disorder (Adverse reactions in at least 5% of patients treated with LAMICTAL as monotherapy and numerically more frequent than in the placebo group are listed by body system with the incidence for LAMICTAL followed by placebo):** Patients in these studies were converted to LAMICTAL (100 to 400 mg/day) or placebo monotherapy from add-on therapy with other psychotropic medications. Patients may have reported multiple adverse reactions during the study; thus, patients may be included in more than one category. **General:** Back pain (8.6); fatigue (8.5), abdominal pain (6.3); **Digestive:** Nausea (14.11%), constipation (5.2%), vomiting (5.2); **Nervous System:** Insomnia (10.6%), somnolence (9.7%), xerostomia (dry mouth) (6.4); **Respiratory:** Rhinitis (7.4%), exacerbation of cough (5.3%), pharyngitis (5.4); **Skin:** Rash (nonserious) (7.5). In the overall bipolar and other mood disorders clinical trials, the rate of serious rash was 0.08% (1 of 1,233) of adult patients who received LAMICTAL as initial monotherapy and 0.13% (2 of 1,538) of adult patients who received LAMICTAL as adjunctive therapy [see *Warnings and Precautions* (5.1)]. Adverse reactions that occurred in at least 5% of patients and were numerically more common during the dose-escalation phase of LAMICTAL in these trials (when patients may have been receiving concomitant medications) compared with the monotherapy phase were: headache (25%), rash (11%), dizziness (10%), diarrhea (8%), dream abnormality (6%), and pruritus (6%). During the monotherapy phase of the double-blind, placebo-controlled trials of 18 months' duration, 13% of 227 patients who received LAMICTAL (100 to 400 mg/day), 16% of 190 patients who received placebo, and 23% of 166 patients who received lithium discontinued therapy because of an adverse reaction. The adverse reactions which most commonly led to discontinuation of LAMICTAL were rash (3%) and mania/hypomania/mixed mood adverse reactions (2%). Approximately 16% of 2,401 patients who received LAMICTAL (50 to 500 mg/day) for Bipolar Disorder in premarketing trials discontinued therapy because of an adverse reaction; most commonly due to rash (5%) and mania/hypomania/mixed mood adverse reactions (2%). The overall adverse reaction profile for LAMICTAL was similar between females and males, between elderly and nonelderly patients, and among racial groups.

These adverse reactions were usually mild to moderate in intensity. Other reactions that occurred in 5% or more patients but equally or more frequently in the placebo group included: dizziness, mania, headache, infection, influenza, pain, accidental injury, diarrhea, and dyspepsia.

Adverse reactions that occurred with a frequency of less than 5% and greater than 1% of patients receiving LAMICTAL and numerically more frequent than placebo were: **General:** Fever, neck pain. **Cardiovascular:** Migraine. **Digestive:** Flatulence. **Metabolic and Nutritional:** Weight gain, edema. **Musculoskeletal:** Arthralgia, myalgia. **Nervous System:** Amnesia, depression, agitation, emotional lability, dyspraxia, abnormal thoughts, dream abnormality, hypoesthesia. **Respiratory:** Sinusitis. **Urogenital:** Urinary frequency.

Adverse Reactions Following Abrupt Discontinuation: In the 2 maintenance trials, there was no increase in the incidence, severity or type of adverse reactions in Bipolar Disorder patients after abruptly terminating therapy with LAMICTAL. In clinical trials in patients with Bipolar Disorder, 2 patients experienced seizures shortly after abrupt withdrawal of LAMICTAL. However, there were confounding factors that may have contributed to the occurrence of seizures in these bipolar patients [see *Warnings and Precautions* (5.9)].

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

6.2 Other Adverse Reactions Observed in All Clinical Trials: LAMICTAL has been administered to 6,694 individuals for whom complete adverse reaction data was captured during all clinical trials, only some of which were placebo controlled. During these trials, all adverse reactions were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse reactions, similar types of adverse reactions were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. The frequencies presented represent the proportion of the 6,694 individuals exposed to LAMICTAL who experienced an event of the type cited on at least one occasion while receiving LAMICTAL. All reported adverse reactions are included except those already listed in the previous tables or elsewhere in the labeling, those too general to be informative, and those not reasonably associated with the use of the drug. Adverse reactions are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse reactions are defined as those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1,000 patients; rare adverse reactions are those occurring in fewer than 1/1,000 patients. **Body as a Whole:** Infrequent: Allergic reaction, chills, and malaise. **Cardiovascular System:** Infrequent: Flushing, hot flashes, hypertension, palpitations, postural hypotension, syncope, tachycardia, and vasodilation. **Dermatological:** Infrequent: Acne, alopecia, hirsutism, maculopapular rash, skin discoloration, and urticaria. **Rare:** Angioedema, erythema, exfoliative dermatitis, fungal dermatitis, herpes zoster, leukoderma, multiforme erythema, petechial rash, pustular rash, Stevens-Johnson syndrome, and vesiculobullous rash. **Digestive System:** Infrequent: Dysphagia, eructation, gastritis, gingivitis, increased appetite, increased salivation, liver function tests abnormal, and mouth ulceration. **Rare:** Gastrointestinal hemorrhage, glossitis, gum hemorrhage, gum hyperplasia, hematemesis, hemorrhagic colitis, hepatitis, melena, stomach ulcer, stomatitis, and tongue edema. **Endocrine System:** **Rare:** Goiter and hypothyroidism. **Hematologic and Lymphatic System:** Infrequent: Eosinophilia and leukopenia. **Rare:** Anemia, eosinophilia, fibrin decrease, fibrinogen decrease, iron deficiency anemia, leukocytosis, lymphocytosis, macrocytic anemia, petechia, and thrombocytopenia. **Metabolic and Nutritional Disorders:** Infrequent: Aspartate transaminase increased. **Rare:** Alcohol intolerance, alkaline phosphatase increase, alanine transaminase increase, bilirubinemia, general edema, gamma glutamyl transpeptidase increase, and hyperglycemia. **Musculoskeletal System:** Infrequent: Arthritis, leg cramps, myasthenia, and twitching. **Rare:** Bursitis, muscle atrophy, pathological fracture, and tendinous contracture. **Nervous System:** Frequent: Confusion and paresthesia. Infrequent: Akathisia, apathy, aphasia, CNS depression, depersonalization, dysarthria, dyskinesia, euphoria, hallucinations, hostility,