

Table 5: Treatment-Emergent Adverse Event Incidence in Placebo-Controlled Adjunctive Trials in Adult Patients with Epilepsy*

Table with 3 columns: Body System/Adverse Experience, Percent of Patients Receiving Adjunctive Lamotrigine Tablets (n=711), Percent of Patients Receiving Adjunctive Placebo (n=419)

* Patients in these adjunctive studies were receiving 1 to 3 of the following concomitant AEDs (carbamazepine, phenytoin, phenobarbital, or primidone) in addition to lamotrigine tablets or placebo. Patients may have received multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category.

† In a randomized, parallel study comparing placebo and 300 and 500 mg/day of lamotrigine tablets, some of the more drug-related adverse events were dose related (see Table 6).

Table 6: Dose-Related Adverse Events from a Randomized, Placebo-Controlled Trial in Adults with Epilepsy

Table with 3 columns: Adverse Experience, Placebo (n=73), Lamotrigine Tablets 300 mg (n=71), Lamotrigine Tablets 500 mg (n=72)

* Significantly greater than placebo group (p < 0.05). † Significantly greater than group receiving lamotrigine tablets 300 mg (p < 0.05).

‡ The overall adverse experience profile for lamotrigine tablets was similar between females and males, and was independent of age. Because the largest non-Caucasian racial subgroup was only 6% of patients receiving lamotrigine tablets in placebo-controlled trials, there are insufficient data to support a statement regarding the distribution of adverse experiences reported by race.

§ Incidence in a Controlled Monotherapy Trial in Adults with Partial Seizures: Table 7 lists treatment-emergent signs and symptoms that occurred in at least 5% of patients with epilepsy treated with monotherapy with lamotrigine tablets in a double-blind, placebo-controlled trial.

Table 7: Treatment-Emergent Adverse Event Incidence in Adults with Partial Seizures in a Controlled Monotherapy Trial*

Table with 3 columns: Body System/Adverse Experience, Percent of Patients Receiving Lamotrigine Tablets (n=43), Percent of Patients Receiving Low-Dose Valproate Monotherapy (n=44)

* Patients in these studies were converted to lamotrigine tablets 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.

† Up to 500 mg/day. Adverse events that occurred with a frequency of less than 5% and greater than 2% of patients receiving lamotrigine tablets and numerically more frequent than placebo were:

Body as a Whole: Asthenia, fever, rectal hemorrhage, peptic ulcer.

Metabolic and Nutritional: Peripheral edema.

Nervous System: Amnesia, ataxia, depression, hypesthesia, libido increase, decreased reflexes, increased restlessness, nystagmus, tremor, weight decrease.

Respiratory: Epistaxis, bronchitis, dyspnea.

Skin and Appendages: Contact dermatitis, dry skin, sweating.

Special Senses: Vision abnormality.

Incidence in Controlled Adjunctive Trials in Pediatric Patients with Epilepsy: Table 8 lists adverse events that occurred in at least 2% of 339 pediatric patients with partial seizures or generalized seizures of Lennox-Gastaut syndrome, who received lamotrigine tablets up to 15 mg/kg per day or a maximum of 750 mg per day.

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

Table with 3 columns: Body System/Adverse Experience, Percent of Patients Receiving Lamotrigine Tablets (n=168), Percent of Patients Receiving Placebo (n=171)

* Patients in these studies were converted to lamotrigine tablets 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.

† Up to 500 mg/day. Adverse events that occurred with a frequency of less than 5% and greater than 2% of patients receiving lamotrigine tablets and numerically more frequent than placebo were:

Body as a Whole: Asthenia, fever, rectal hemorrhage, peptic ulcer.

Metabolic and Nutritional: Peripheral edema.

Nervous System: Amnesia, ataxia, depression, hypesthesia, libido increase, decreased reflexes, increased restlessness, nystagmus, tremor, weight decrease.

Respiratory: Epistaxis, bronchitis, dyspnea.

Skin and Appendages: Contact dermatitis, dry skin, sweating.

Special Senses: Vision abnormality.

Incidence in Controlled Adjunctive Trials in Pediatric Patients with Epilepsy: Table 9 lists adverse events that occurred in at least 2% of 339 pediatric patients with partial seizures or generalized seizures of Lennox-Gastaut syndrome, who received lamotrigine tablets up to 15 mg/kg per day or a maximum of 750 mg per day.

Table 9: Treatment-Emergent Adverse Event Incidence in 2 Placebo-Controlled Trials in Adults with Bipolar I Disorder*

Table with 3 columns: Body System/Adverse Experience, Percent of Patients Receiving Lamotrigine Tablets (n=227), Percent of Patients Receiving Placebo (n=190)

* Patients in these studies were converted to lamotrigine tablets (100 to 400 mg/day) or placebo monotherapy from add-on therapy with other psychotropic medications. Patients may have reported multiple adverse experiences during the study; thus, patients may be included in more than one category.

† Adverse experiences reported by at least 5% of patients are included.

‡ In the overall bipolar and other mood disorders clinical trials, the rate of serious rash was 0.06% (1 of 1,233) of adults who received lamotrigine tablets as initial monotherapy and 0.13% (2 of 1,538) of adults who received lamotrigine tablets as adjunctive therapy (see WARNINGS).

§ These adverse experiences were usually mild to moderate in intensity.

¶ Other events that occurred in 5% or more patients but equally or more frequently in the placebo group included: dizziness, mania, headache, infection, influenza, pain, accidental injury, diarrhea, and dyspepsia.

‡ Adverse events that occurred with a frequency of less than 5% and greater than 1% of patients receiving lamotrigine tablets and numerically more frequent than placebo were:

Body as a Whole: Fever, neck pain.

Cardiovascular System: Myocardial infarction.

Digestive: Flatulence.

Metabolic and Nutritional: Weight gain, edema.

Musculoskeletal: Arthralgia, myalgia.

Nervous System: Amnesia, depression, agitation, emotional lability, dyspraxia, abnormal thoughts, dream abnormality, hyposthesia.

Respiratory: Sinusitis.

Urogenital: Urinary frequency.

Adverse Events Following Abrupt Discontinuation: In the 2 maintenance trials, there was no increase in the incidence, severity or type of adverse events in Bipolar Disorder patients after abruptly terminating lamotrigine therapy. In clinical trials in patients with Bipolar Disorder, 2 patients experienced seizures shortly after abrupt withdrawal of lamotrigine tablets. However, there were confounding factors that may have contributed to the occurrence of these seizures in these bipolar patients (see DOSAGE AND ADMINISTRATION).

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

‡ The overall adverse event profile for lamotrigine tablets was similar between females and males, between elderly and non-elderly patients, and among racial groups.

§ Other Adverse Events Observed During All Clinical Trials For Pediatric and Adult Patients with Epilepsy or Bipolar Disorder and Other Mood Disorders: Lamotrigine tablets have been administered to 6,694 individuals for whom complete adverse event data was captured during this clinical trial, 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 facilitate comparison of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. The frequencies presented represent the proportion of the 6,694 individuals exposed to lamotrigine tablets who experienced each of the type coded on the list.

¶ Similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. The frequencies presented represent the proportion of the 6,694 individuals exposed to lamotrigine tablets who experienced each of the type coded on the list.

‡ Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: very common (≥ 10%), common (≥ 1%), uncommon (≥ 0.1%), rare (≥ 0.01%), very rare (≥ 0.001%).

§ Body as a Whole: Infection, allergic reaction, chills, halitosis, and malaise.

¶ Infection: Abdomen enlarged, abscess, and scudicide/sulfonamide attempt.

‡ Cardiovascular System: Infection: Flushing, hot flashes, hypertension, palpitations, postural hypotension, syncope, tachycardia, and vasodilation.

§ Rare: Angina pectoris, atrial fibrillation, deep thrombophlebitis, ECG abnormality, and myocardial infarction.

¶ Dermatology: Infection: Acne, alopecia, hirsutism, maculopapular rash, skin discoloration, and urticaria.

‡ Rare: Angioedema, erythema, exfoliative dermatitis, fungal dermatitis, herpes zoster, leukoderma, polymorphous erythema, petechial rash, pustular rash, seborrhea, Stevens-Johnson syndrome, and vesiculobullous rash.

§ Digestive System: Infection: 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 ache, stomatitis, thirst, and tongue edema.

‡ Endocrine System: Rare: Gout and hyperthyroidism.

§ Hematologic and Lymphatic System: Infection: Echinocystis and leukopenia.

¶ Rare: Anemia, eosinophilia, fibrin decrease, fibrinogen decrease, iron deficiency anemia, leukocytosis, lymphocytosis, macrocytic anemia, petechia, and thrombocytopenia.

‡ Metabolic and Nutritional Disorders: Infection: Aspartate transaminase increased.

§ Rare: Alcohol intolerance, alkaline phosphatase increase, alanine transaminase increase, bilirubinemia, genital edema, gamma glutamyl transpeptidase increase, and hyperglycemia.

¶ Musculoskeletal System: Infection: Arthritis, leg cramps, myasthenia, and twitching.

‡ Rare: Bursitis, joint disorder, muscle atrophy, pathological fracture, and tendinous contracture.

§ Nervous System: Infection: Confusion and paresthesia.

¶ Rare: Akathisia, apathy, aphasia, CNS depression, depersonalization, dysarthria, dyskinesia, euphoria, hallucinations, hostility, hyperkinesia, hypotonia, libido decrease, memory decrease, mild racing, movement disorder, myoclonus, panic attack, paranoid reaction, personality disorder, psychosis, sleep disorder, stupor, and suicidal ideation.

‡ Rare: Cerebellar syndrome, cerebrovascular accident, cerebral sinus thrombosis, choreoathetosis, CNS stimulation, delirium, delusions, dystonia, extrapyramidal syndrome, faintness, grand mal convulsions, hemiplegia, hyperreflexia, hypotonia, hypokinesia, hypomania, manic depression reaction, muscle spasms, neuralgia, neuritis, paralytic, and periphrasias.

§ Respiratory System: Infection: Yawn.

¶ Rare: Hiccups and hyperventilation.

‡ Special Senses: Infection: Amblyopia.

§ Infection: Abnormality of accommodation, conjunctivitis, dry eyes, ear pain, photophobia, taste perversion, and vertigo.

¶ Rare: Deafness, lacrimation disorder, oscillopsia, parosmia, ptosis, strabismus, taste loss, uvulitis, and visual field defect.

‡ Urogenital System: Infection: Abnormal ejaculation, breast pain, hematuria, impotence, menorrhagia, polyuria, urinary incontinence, and urine abnormalities.

§ Rare: Acute kidney failure, anorexia, breast abscess, breast neoplasm, creatinine increase, cystitis, dysuria, epididymitis, female lactation, kidney failure, kidney pain, nocturia, urinary urgency, urinary incontinence, and vaginal moniliasis.

¶ Postmarketing and Other Experience: In addition to the adverse experiences reported during clinical testing of lamotrigine tablets, the following adverse experiences have been reported in patients receiving marketed lamotrigine tablets and in controlled clinical trials. The adverse experiences listed below are not necessarily related to lamotrigine tablets, and data are insufficient to support an estimate of their incidence or to establish causation.

‡ Blood and Lymphatic: Arteriovenous anastomosis, aplastic anemia, disseminated intravascular coagulation, hemolytic anemia, neutropenia, pancytopenia, red cell aplasia.

§ Gastrointestinal: Esophagitis.

¶ Hematology: Test and Pancreas: Pancreatitis.

‡ Immunology: Lupus-like reaction, vasculitis.

§ Lower Respiratory: Agranulocytosis.

¶ Musculoskeletal: Rhabdomyolysis has been observed in patients experiencing hypersensitivity reactions.

‡ Neurology: Exacerbation of parkinsonism symptoms in patients with pre-existing Parkinson's disease, tics.

§ Non-site Specific: Hypersensitivity reaction, multiorgan failure, progressive immunosuppression.

¶ DRUG ABUSE AND DEPENDENCE The abuse and dependence potential of lamotrigine tablets have not been evaluated in human studies.

‡ OVERDOSAGE Human Overdose Experience: Overdoses involving quantities up to 15 g have been reported for lamotrigine tablets, some of which have been fatal. Overdose has resulted in ataxia, nystagmus, increased seizures, decreased level of consciousness, coma, and intraventricular conduction delay.

§ Management of Overdose: There are no specific antidotes for lamotrigine tablets. 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 within the usual time period to protect the airway. It should be kept in mind that lamotrigine is rapidly absorbed (see CLINICAL PHARMACOLOGY). It is uncertain whether hemodialysis is an effective means of removing lamotrigine from the blood. In 6 renal failure patients, about 20% of the amount of lamotrigine in the body was removed by hemodialysis during a 4-hour session. The Control Center should be contacted for information on the management of overdoses of lamotrigine tablets.

¶ DOSAGE AND ADMINISTRATION Epilepsy: Adjunctive Use: Lamotrigine tablets are indicated as adjunctive therapy for partial seizures, the generalized tonic-clonic seizures of Lennox-Gastaut syndrome in adults and pediatric patients (≥ 2 years of age).

‡ Monotherapy Use: Lamotrigine tablets are indicated for conversion to monotherapy in adults with partial seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single AED.

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

¶ Bipolar Disorder: Lamotrigine tablets are indicated for the maintenance treatment of Bipolar I Disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy. The effectiveness of lamotrigine tablets in the acute treatment of mood episodes has not been established.

‡ General Dosing Considerations for Epilepsy and Bipolar Disorder Patients: The risk of nonserious rash is increased when the recommended initial dose and/or the rate of dose escalation of lamotrigine tablets is exceeded. There are suggestions, yet to be proven, that the risk of severe, potentially life-threatening rash may be increased by (1) co-administration of lamotrigine tablets with valproate, (2) exceeding the recommended initial dose of lamotrigine tablets, or (3) exceeding the recommended dose escalation for lamotrigine tablets. However, cases have been reported in the absence of these factors (see BOX WARNING). Therefore, it is important that the dosing recommendations be followed closely.

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

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

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

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

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consistently occur during the "pill-free" week, dose adjustments to the overall maintenance dose may be necessary. Dose adjustments limited to the "pill-free" week are not recommended. For women taking lamotrigine tablets in addition to carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, no adjustment should be necessary to the dose of lamotrigine tablets. (f) Stopping Estrogen-Containing Oral Contraceptives: For women not taking carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, the maintenance dose of lamotrigine tablets will in most cases need to be decreased by as much as 50%, in order to maintain a consistent lamotrigine plasma level. The decrease in dose of lamotrigine tablets should not exceed 25% of the total daily dose per week over a 2-week period unless clinical response or lamotrigine plasma levels indicate otherwise (see PRECAUTIONS: Drug Interactions). For women taking lamotrigine tablets in addition to carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, no adjustment to the dose of lamotrigine tablets should be necessary.

Women and Other Hormonal Contraceptive Preparations or Hormone Replacement Therapy: The effect of other hormonal contraceptive preparations or hormone replacement therapy on the pharmacokinetics of lamotrigine has not been systematically evaluated. It has been reported that ethinylstradiol, 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 dose of lamotrigine tablets in the presence of progestogens alone will likely not be needed. Patients With Hepatic Impairment: Experience in patients with hepatic impairment is limited. Based on a clinical pharmacology study in 24 patients with mild, moderate, and severe liver dysfunction (see CLINICAL PHARMACOLOGY), the following general recommendations can be made. No dosage adjustment is needed in patients with mild liver impairment. Escalation, and maintenance doses may be reduced by approximately 25% in patients with moderate and severe liver impairment without ascites and 50% in patients with severe liver impairment with ascites. Escalation and maintenance doses may be adjusted according to clinical response.

Patients with Renal Function Impairment: Initial doses of lamotrigine tablets should be based on patients' AED regimen (see PRECAUTIONS: Drug Interactions). Few patients with severe renal impairment have been evaluated during chronic treatment with lamotrigine tablets. Because there is inadequate experience in this population, lamotrigine tablets should be used with caution in these patients.

Special Populations: The following general recommendations for the pharmacokinetics of lamotrigine has not been systematically evaluated. It has been reported that ethinylstradiol, 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 dose of lamotrigine tablets in the presence of progestogens alone will likely not be needed. Patients With Hepatic Impairment: Experience in patients with hepatic impairment is limited. Based on a clinical pharmacology study in 24 patients with mild, moderate, and severe liver dysfunction (see CLINICAL PHARMACOLOGY), the following general recommendations can be made. No dosage adjustment is needed in patients with mild liver impairment. Escalation, and maintenance doses may be reduced by approximately 25% in patients with moderate and severe liver impairment without ascites and 50% in patients with severe liver impairment with ascites. Escalation and maintenance doses may be adjusted according to clinical response.

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