PRODUCT NAME	:	LAMOTRIGINE tablets USP	COUNTRY : US	LOCATION : -		Supersedes A/W No.:		V. No.: 01
ITEM / PACK	:	Outsert	NO. OF COLORS: 1	REMARK :				
DESIGN STYLE	:	Front Side	PANTONE SHADE NOS.:	SUBSTRATE : 40 g/m2 Bible Paper				
CODE	:	8096631		Activities	Department	Name	Signature	Date
DIMENSIONS (MM)	:	640 x 510		Prepared By	Pkg.Dev			
ART WORK SIZE	:	S/S	Black	Reviewed By	Pkg.Dev			
DATE	:	27-08-2024	Font Size 6 pt	Approved By	Quality			

4188

Note: Pharma code/ Bar code and adjacent text must be visible on folded leaflet.
These details can be moved by printed to arrange pharma code/ Bar code and adjacent text visible on folded leaflet.

4188

LAMOTRIGINE tablets USP, for oral use

08096631

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LAMOTRIGINE TABLETS safely and effectively. See full prescribing information for LAMOTRIGINE TABLETS.

LAMOTRIGINE tablets, for oral use
Initial U.S. Approval: 1994

WARNING: SERIOUS SKIN RASHES
See full prescribing information for complete boxed warning.

- **Cases of life-threatening serious rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis, and/or rash-related death have been caused by lamotrigine. The rate of serious rash is greater in pediatric patients than in adults. Additional factors that may increase the risk of rash include:**
  - **coadministration with valproate.**
  - **exceeding recommended initial dose of lamotrigine.**
  - **exceeding recommended dose escalation for lamotrigine. (5.1)**
- **Benign rashes are also caused by lamotrigine; however, it is not possible to predict which rashes will prove to be serious or life threatening. Lamotrigine should be discontinued at the first sign of rash, unless the rash is clearly not drug related. (5.1)**

RECENT MAJOR CHANGES

Warnings and Precautions, Cardiac Rhythm and Conduction Abnormalities (5.4) 3/2021

INDICATIONS AND USAGE

Lamotrigine tablet is indicated for:

Epilepsy-adjunctive therapy in patients aged 2 years and older:

- partial-onset seizures.
- primary generalized tonic-clonic seizures.
- generalized seizures of Lennox-Gastaut syndrome. (1.1)

Epilepsy-monotherapy in patients aged 16 years and older: Conversion to monotherapy in patients with partial-onset seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single antiepileptic drug. (1.1)

Bipolar disorder: Maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy. (1.2)

Limitations of Use: Treatment of acute manic or mixed episodes is not recommended. Effectiveness of lamotrigine in the acute treatment of mood episodes has not been established.

DOSAGE AND ADMINISTRATION

- Dosing is based on concomitant medications, indication, and patient age. (2.1, 2.2, 2.3, 2.4)
- To avoid an increased risk of rash, the recommended initial dose and subsequent dose escalations should not be exceeded. Lamotrigine Tablets Starter Kits are available for the first 5 weeks of treatment. (2.1, 16)
- Do not restart lamotrigine tablets in patients who discontinued due to rash unless the potential benefits clearly outweigh the risks. (2.1, 5.1)
- Adjustments to maintenance doses will be necessary in most patients starting or stopping estrogen-containing oral contraceptives. (2.1, 5.9)
- Discontinuation: Taper over a period of at least 2 weeks (approximately 50% dose reduction per week). (2.1, 5.10)

Epilepsy:

- Adjunctive therapy-See Table 1 for patients older than 12 years and Tables 2 and 3 for patients aged 2 to 12 years. (2.2)
- Conversion to monotherapy-See Table 4. (2.3)

Bipolar disorder: See Tables 5 and 6. (2.4)

DOSAGE FORMS AND STRENGTHS

- Tablets: 25 mg, 100 mg, 150 mg, and 200 mg; scored. (3.1, 16)

CONTRAINDICATIONS

Hypersensitivity to the drug or its ingredients. (Boxed Warning, 4)

WARNINGS AND PRECAUTIONS

- Life-threatening serious rash and/or rash-related death: Discontinue at the first sign of rash, unless the rash is clearly not drug related. (Boxed Warning, 5.1)
- Hemophagocytic lymphohistiocytosis: Consider this diagnosis and evaluate patients immediately if they develop signs or symptoms of systemic inflammation. Discontinue lamotrigine tablets if an alternative etiology is not established. (5.2)
- Fatal or life-threatening hypersensitivity reaction: Multiorgan hypersensitivity reactions, also known as drug reaction with eosinophilia and systemic symptoms, may be fatal or life threatening. Early signs may include rash, fever, and lymphadenopathy. These reactions may be associated with other organ involvement, such as hepatitis, hepatic failure, blood dyscrasias, or acute multiorgan failure. Lamotrigine tablets should be discontinued if alternate etiology for this reaction is not found. (5.3)
- Cardiac rhythm and conduction abnormalities: Based on in vitro findings, lamotrigine tablets could cause serious arrhythmias and/or death in patients with certain underlying cardiac disorders or arrhythmias. Any expected or observed benefit of lamotrigine tablets in an individual patient with clinically important structural or functional heart disease must be carefully weighed against the risk for serious arrhythmias and/or death for that patient. (5.4)
- Blood dyscrasias (e.g., neutropenia, thrombocytopenia, pancytopenia): May occur, either with or without an associated hypersensitivity syndrome. Monitor for signs of anemia, unexpected infection, or bleeding. (5.5)
- Suicidal behavior and ideation: Monitor for suicidal thoughts or behaviors. (5.6)
- Aseptic meningitis: Monitor for signs of meningitis. (5.7)
- Medication errors due to product name confusion: Strongly advise patients to visually inspect tablets to verify the received drug is correct. (5.8, 16, 17)

ADVERSE REACTIONS

Epilepsy: Most common adverse reactions (incidence ≥10%) in adults were dizziness, headache, diplopia, ataxia, nausea, blurred vision, somnolence, rhinitis, pharyngitis, and rash. Additional adverse reactions (incidence ≥10%) reported in children included vomiting, infection, fever, accidental injury, diarrhea, abdominal pain, and tremor. (6.1)

Bipolar disorder: Most common adverse reactions (incidence >5%) in adults were nausea, insomnia, somnolence, back pain, fatigue, rash, rhinitis, abdominal pain, and xerostomia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Torrent Pharma Inc. at 1-800-912-9561 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Valproate increases lamotrigine concentrations more than 2-fold. (7, 12.3)
- Carbamazepine, phenytoin, phenobarbital, primidone, and rifampin decrease lamotrigine concentrations by approximately 40%. (7, 12.3)
- Estrogen-containing oral contraceptives decrease lamotrigine concentrations by approximately 50%. (7, 12.3)
- Protease inhibitors lopinavir/ritonavir and atazanavir/lopinavir decrease lamotrigine exposure by approximately 50% and 32%, respectively. (7, 12.3)
- Coadministration with organic cationic transporter 2 substrates with narrow therapeutic index is not recommended (7, 12.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data may cause fetal harm. (8.1)
- Hepatic impairment: Dosage adjustments required in patients with moderate and severe liver impairment. (2.1, 8.6)
- Renal impairment: Reduced maintenance doses may be effective for patients with significant renal impairment. (2.1, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS SKIN RASHES

Lamotrigine can cause serious rashes requiring hospitalization and discontinuation of treatment. The incidence of these rashes, which have included Stevens-Johnson syndrome, is approximately 0.3% to 0.8% in pediatric patients (aged 2 to 17 years) and 0.08% to 0.3% in adults receiving lamotrigine. One rash-related death was reported in a prospectively followed cohort of 1,983 pediatric patients (aged 2 to 16 years) with epilepsy taking lamotrigine as adjunctive therapy. 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 lamotrigine. There are suggestions, yet to be proven, that the risk of rash may also be increased by (1) coadministration of lamotrigine with valproate (includes valproic acid and divalproex sodium), (2) exceeding the recommended initial dose of lamotrigine, or (3) exceeding the recommended dose escalation for lamotrigine. However, cases have occurred in the absence of these factors.

Nearly all cases of life-threatening rashes caused by lamotrigine 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 lamotrigine, it is not possible to predict reliably which rashes will prove to be serious or life threatening. Accordingly, lamotrigine 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)]*.

1 INDICATIONS AND USAGE

1.1 Epilepsy

Adjunctive Therapy

Lamotrigine tablets are indicated as adjunctive therapy for the following seizure types in patients aged 2 years and older:

- partial-onset seizures.
- primary generalized tonic-clonic (PGTC) seizures.
- generalized seizures of Lennox-Gastaut syndrome.

Monotherapy

Lamotrigine tablets are indicated for conversion to monotherapy in adults (aged 16 years and older) with partial-onset seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single antiepileptic drug (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 simultaneous conversion to monotherapy from 2 or more concomitant AEDs.

1.2 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 *[see Clinical Studies (14.2)]*.

Limitations of Use

Treatment of acute manic or mixed episodes is not recommended. Effectiveness of lamotrigine tablets in the acute treatment of mood episodes has not been established.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Considerations

Rash

There are suggestions, yet to be proven, that the risk of severe, potentially life-threatening rash may be increased by (1) coadministration 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 occurred in the absence of these factors *[see Boxed Warning]*. Therefore, it is important that the dosing recommendations be followed closely.

The risk of nonserious rash may be increased when the recommended initial dose and/or the rate of dose escalation for lamotrigine tablets is exceeded and in patients with a history of allergy or rash to other AEDs.

Lamotrigine Tablets Starter Kits provide lamotrigine at doses consistent with the recommended titration schedule for the first 5 weeks of treatment, based upon concomitant medications, for patients with epilepsy (older than 12 years) and bipolar I disorder (adults) and are intended to help reduce the potential for rash. The use of lamotrigine Starter Kits is recommended for appropriate patients who are starting or restarting lamotrigine *[see How Supplied/Storage and Handling (16)]*.

It is recommended that lamotrigine tablets not be restarted in patients who discontinued due to rash associated with prior treatment with lamotrigine 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 for a period of more than 5 half-lives, it is recommended that initial dosing recommendations and guidelines be followed. The half-life of lamotrigine is affected by other concomitant medications *[see Clinical Pharmacology (12.3)]*.

Lamotrigine Added to Drugs Known to Induce or Inhibit Glucuronidation

Because lamotrigine is metabolized predominantly by glucuronic acid conjugation, drugs that are known to induce or inhibit glucuronidation may affect the apparent clearance of lamotrigine. Drugs that induce glucuronidation include carbamazepine, phenytoin, phenobarbital, primidone, rifampin, estrogen-containing oral contraceptives, and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir. Valproate inhibits glucuronidation. For dosing considerations for lamotrigine in patients on estrogen-containing contraceptives and atazanavir/ritonavir, see below and Table 13. For dosing considerations for lamotrigine in patients on other drugs known to induce or inhibit glucuronidation, see Tables 1, 2, 5-6, and 13.

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 *[see Clinical Pharmacology (12.3)]*.

Women Taking Estrogen-Containing Oral Contraceptives

Starting Lamotrigine Tablets in Women Taking Estrogen-Containing Oral Contraceptives: Although estrogen-containing oral contraceptives have been shown to increase the clearance of lamotrigine *[see Clinical Pharmacology (12.3)]*, no adjustments to the recommended dose-escalation guidelines for lamotrigine should be necessary solely based on the use of estrogen-containing oral contraceptives. Therefore, dose escalation should follow the recommended guidelines for initiating adjunctive therapy with lamotrigine tablets based on the concomitant AED or other concomitant medications (see Tables 1, 5, and 7). See below for adjustments to maintenance doses of lamotrigine in women taking estrogen-containing oral contraceptives.

Adjustments to the Maintenance Dose of Lamotrigine Tablets in Women Taking Estrogen-Containing Oral Contraceptives:

(1) Taking Estrogen-Containing Oral Contraceptives: In women not taking carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir that induce lamotrigine glucuronidation *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*, the maintenance dose of lamotrigine will in most cases need to be increased by as much as 2-fold over the recommended target maintenance dose to maintain a consistent lamotrigine plasma level.

[illegible]

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PRODUCT NAME	:	LAMOTRIGINE tablets USP	COUNTRY : US	LOCATION : -		Supersedes A/W No.:		V. No.: 01
ITEM / PACK	:	Outsert	NO. OF COLORS: 1	REMARK :				
DESIGN STYLE	:	Back Side	PANTONE SHADE NOS.:	SUBSTRATE : 40 g/m2 Bible Paper				
CODE	:	8096631		Activities	Department	Name	Signature	Date
DIMENSIONS (MM)	:	640 x 510		Prepared By	Pkg.Dev			
ART WORK SIZE	:	S/S	Black	Reviewed By	Pkg.Dev			
DATE	:	27-08-2024	Font Size 6 pt	Approved By	Quality			

Note: Pharma code/ Bar code and adjacent text must be visible on folded leaflet.
These details can be moved by printed to arrange pharma code/ Bar code and adjacent text visible on folded leaflet.

Rare: Acute kidney failure, anorgasmia, breast abscess, breast neoplasm, creatinine increase, cystitis, dysuria, epididymitis, female lactation, kidney failure, kidney pain, nocturia, urinary retention, urinary urgency.

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of lamotrigine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic

Agranulocytosis, hemolytic anemia, lymphadenopathy not associated with hypersensitivity disorder.

Gastrointestinal

Esophagitis.

Hepatobiliary Tract and Pancreas

Pancreatitis.

Immunologic

Hypogammaglobulinemia, lupus-like reaction, vasculitis.

Lower Respiratory

Apnea.

Musculoskeletal

Rhabdomyolysis has been observed in patients experiencing hypersensitivity reactions.

Nervous System

Aggression, exacerbation of Parkinsonian symptoms in patients with pre-existing Parkinson's disease, tics.

Non-site Specific

Progressive immunosuppression.

Renal and Urinary Disorders

Tubulointerstitial nephritis (has been reported alone and in association with uveitis).

7 DRUG INTERACTIONS

Significant drug interactions with lamotrigine are summarized in this section.

Uridine 5´-diphospho-glucuronyl transferases (UGT) have been identified as the enzymes responsible for metabolism of lamotrigine. Drugs that induce or inhibit glucuronidation may, therefore, affect the apparent clearance of lamotrigine. Strong or moderate inducers of the cytochrome P450 3A4 (CYP3A4) enzyme, which are also known to induce UGT, may also enhance the metabolism of lamotrigine.

Those drugs that have been demonstrated to have a clinically significant impact on lamotrigine metabolism are outlined in Table 13. Specific dosing guidance for these drugs is provided in the Dosage and Administration section *[see Dosage and Administration (2.1)]*.

Additional details of these drug interaction studies are provided in the Clinical Pharmacology section *[see Clinical Pharmacology (12.3)]*.

Table 13. Established and Other Potentially Significant Drug Interactions

Concomitant Drug	Effect on Concentration of Lamotrigine or Concomitant Drug	Clinical Comment
Estrogen-containing oral contraceptive preparations containing 30 mcg ethinylestradiol and 150 mcg levonorgestrel	↓ lamotrigine ↓ levonorgestrel	Decreased lamotrigine concentrations approximately 50%. Decrease in levonorgestrel component by 19%.
Carbamazepine and carbamazepine epoxide	↓ lamotrigine ? carbamazepine epoxide	Addition of carbamazepine decreases lamotrigine concentration approximately 40%. May increase carbamazepine epoxide levels.
Lopinavir/ritonavir	↓ lamotrigine	Decreased lamotrigine concentration approximately 50%.
Atazanavir/ritonavir	↓ lamotrigine	Decreased lamotrigine AUC approximately 32%.
Phenobarbital/primidone	↓ lamotrigine	Decreased lamotrigine concentration approximately 40%.
Phenytoin	↓ lamotrigine	Decreased lamotrigine concentration approximately 40%.
Rifampin	↓ lamotrigine	Decreased lamotrigine AUC approximately 40%.
Valproate	↑ lamotrigine ? valproate	Increased lamotrigine concentrations slightly more than 2-fold. There are conflicting study results regarding effect of lamotrigine on valproate concentrations: 1) a mean 25% decrease in valproate concentrations in healthy volunteers, 2) no change in valproate concentrations in controlled clinical trials in patients with epilepsy.

↓= Decreased (induces lamotrigine glucuronidation).
↑= Increased (inhibits lamotrigine glucuronidation).
? = Conflicting data.

Effect of Lamotrigine on Organic Cationic Transporter 2 Substrates

Lamotrigine is an inhibitor of renal tubular secretion via organic cationic transporter 2 (OCT2) proteins *[see Clinical Pharmacology (12.3)]*. This may result in increased plasma levels of certain drugs that are substantially excreted via this route. Coadministration of lamotrigine with OCT2 substrates with a narrow therapeutic index (e.g., dofetilide) is not recommended.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to AEDs, including lamotrigine, during pregnancy. Encourage women who are taking lamotrigine during pregnancy to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry by calling 1-888-233-2334 or visiting http://www.aedpregnancyregistry.org/.

Risk Summary

Data from several prospective pregnancy exposure registries and epidemiological studies of pregnant women have not detected an increased frequency of major congenital malformations or a consistent pattern of malformations among women exposed to lamotrigine compared with the general population *(see Data)*. The majority of lamotrigine pregnancy exposure data are from women with epilepsy. In animal studies, administration of lamotrigine during pregnancy resulted in developmental toxicity (increased mortality, decreased body weight, increased structural variation, neurobehavioral abnormalities) at doses lower than those administered clinically.

Lamotrigine decreased fetal folate concentrations in rats, an effect known to be associated with adverse pregnancy outcomes in animals and humans *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

As with other AEDs, physiological changes during pregnancy may affect lamotrigine concentrations and/or therapeutic effect. There have been reports of decreased lamotrigine concentrations during pregnancy and restoration of pre-pregnancy concentrations after delivery. Dose adjustments may be necessary to maintain clinical response.

Data

Human Data: Data from several international pregnancy registries have not shown an increased risk for malformations overall. The International Lamotrigine Pregnancy Registry reported major congenital malformations in 2.2% (95% CI: 1.6%, 3.1%) of 1,558 infants exposed to lamotrigine monotherapy in the first trimester of pregnancy. The NAAED Pregnancy Registry reported major congenital malformations among 2.0% of 1,562 infants exposed to lamotrigine monotherapy in the first trimester. EURAP, a large international pregnancy registry focused outside of North America, reported major birth defects in 2.9% (95% CI: 2.3%, 3.7%) of 2,514 exposures to lamotrigine monotherapy in the first trimester. The frequency of major congenital malformations was similar to estimates from the general population.

The NAAED Pregnancy Registry observed an increased risk of isolated oral clefts: among 2,200 infants exposed to lamotrigine early in pregnancy, the risk of oral clefts was 3.2 per 1,000 (95% CI: 1.4, 6.3), a 3-fold increased risk versus unexposed healthy controls. This finding has not been observed in other large international pregnancy registries. Furthermore, a case-control study based on 21 congenital anomaly registries covering over 10 million births in Europe reported an adjusted odds ratio for isolated oral clefts with lamotrigine exposure of 1.45 (95% CI: 0.8, 2.63).

Several meta-analyses have not reported an increased risk of major congenital malformations following lamotrigine exposure in pregnancy compared with healthy and disease-matched controls. No patterns of specific malformation types were observed.

The same meta-analyses evaluated the risk of additional maternal and infant outcomes including fetal death, stillbirth, preterm birth, small for gestational age, and neurodevelopmental delay. Although there are no data suggesting an increased risk of these outcomes with lamotrigine monotherapy exposure, differences in outcome definition, ascertainment methods, and comparator groups limit the conclusions that can be drawn.

Animal Data: When lamotrigine was administered to pregnant mice, rats, or rabbits during the period of organogenesis (oral doses of up to 125, 25, and 30 mg/kg, respectively), reduced fetal body weight and increased incidences of fetal skeletal variations were seen in mice and rats at doses that were also maternally toxic. The no-effect doses for embryofetal developmental toxicity in mice, rats, and rabbits (75, 6.25, and 30 mg/kg, respectively) are similar to (mice and rabbits) or less than (rats) the human dose of 400 mg/day on a body surface area (mg/m^2) basis.

In a study in which pregnant rats were administered lamotrigine (oral doses of 0, 5, or 25 mg/kg) during the period of organogenesis and offspring were evaluated postnatally, neurobehavioral abnormalities were observed in exposed offspring at both doses. The lowest effect dose for developmental neurotoxicity in rats is less than the human dose of 400 mg/day on a mg/m^2 basis. Maternal toxicity was observed at the higher dose tested.

When pregnant rats were administered lamotrigine (oral doses of 0, 5, 10, or 20 mg/kg) during the latter part of gestation and throughout lactation, increased offspring mortality (including stillbirths) was seen at all doses. The lowest effect dose for pre- and post-natal developmental toxicity in rats is less than the human dose of 400 mg/day on a mg/m^2 basis. Maternal toxicity was observed at the 2 highest doses tested.

When administered to pregnant rats, lamotrigine decreased fetal folate concentrations at doses greater than or equal to 5 mg/kg/day, which is less than the human dose of 400 mg/day on a mg/m^2 basis.

8.2 Lactation

Risk Summary

Lamotrigine is present in milk from lactating women taking lamotrigine tablets *(see Data)*. Neonates and young infants are at risk for high serum levels because maternal serum and milk levels can rise to high levels postpartum if lamotrigine dosage has been increased during pregnancy but is not reduced after delivery to the pre-pregnancy dosage. Glucuronidation is required for drug clearance. Glucuronidation capacity is immature in the infant and this may also contribute to the level of lamotrigine exposure. Events including rash, apnea, drowsiness, poor sucking, and poor weight gain (requiring hospitalization in some cases) have been reported in infants who have been human milk-fed by mothers using lamotrigine; whether or not these events were caused by lamotrigine is unknown. No data are available on the effects of the drug on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for lamotrigine and any potential adverse effects on the breastfed infant from lamotrigine or from the underlying maternal condition.

Clinical Considerations

Human milk-fed infants should be closely monitored for adverse events resulting from lamotrigine. Measurement of infant serum levels should be performed to rule out toxicity if concerns arise. Human milk-feeding should be discontinued in infants with lamotrigine toxicity.

Data

Data from multiple small studies indicate that lamotrigine plasma levels in nursing infants have been reported to be as high as 50% of maternal plasma concentrations.

8.4 Pediatric Use

Epilepsy

Lamotrigine is indicated as adjunctive therapy in patients aged 2 years and older for partial-onset seizures, the generalized seizures of Lennox-Gastaut syndrome, and PGTC seizures.

Safety and efficacy of lamotrigine used as adjunctive treatment for partial-onset seizures were not demonstrated in a small, randomized, double-blind, placebo-controlled withdrawal trial in very young pediatric patients (aged 1 to 24 months). Lamotrigine was associated with an increased risk for infectious adverse reactions (Lamotrigine 37%, placebo 5%), and respiratory adverse reactions (Lamotrigine 26%, placebo 5%). Infectious adverse reactions included bronchiolitis, bronchitis, ear infection, eye infection, otitis externa, pharyngitis, urinary tract infection, and viral infection. Respiratory adverse reactions included nasal congestion, cough, and apnea.

Bipolar Disorder

Safety and efficacy of lamotrigine for the maintenance treatment of bipolar disorder were not established in a double-blind, randomized withdrawal, placebo-controlled trial that evaluated 301 pediatric patients aged 10 to 17 years with a current manic/hypomanic, depressed, or mixed mood episode as defined by DSM-IV-TR. In the randomized phase of the trial, adverse reactions that occurred in at least 5% of patients taking lamotrigine (n = 87) and were twice as common compared with patients taking placebo (n = 86) were influenza (lamotrigine 8%, placebo 2%), oropharyngeal pain (lamotrigine 8%, placebo 2%), vomiting (lamotrigine 6%, placebo 2%), contact dermatitis (lamotrigine 5%, placebo 2%), upper abdominal pain (lamotrigine 5%, placebo 1%), and suicidal ideation (lamotrigine 5%, placebo 0%).

Juvenile Animal Data

In a juvenile animal study in which lamotrigine (oral doses of 0, 5, 15, or 30 mg/kg) was administered to young rats from postnatal day 7 to 62, decreased viability and growth were seen at the highest dose tested and long-term neurobehavioral abnormalities (decreased locomotor activity, increased reactivity, and learning deficits in animals tested as adults) were observed at the 2 highest doses. The no-effect dose for adverse developmental effects in juvenile animals is less than the human dose of 400 mg/day on a mg/m^2 basis.

8.5 Geriatric Use

Clinical trials of lamotrigine for epilepsy and bipolar disorder did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients or exhibit a different safety profile than that of younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

Experience in patients with hepatic impairment is limited. Based on a clinical pharmacology study in 24 subjects with mild, moderate, and severe liver impairment *[see Clinical Pharmacology (12.3)]*, the following general recommendations can be made. No dosage adjustment is needed in patients with mild liver impairment. Initial, escalation, and maintenance doses should generally 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 *[see Dosage and Administration (2.1)]*.

8.7 Renal Impairment

Lamotrigine is metabolized mainly by glucuronic acid conjugation, with the majority of the metabolites being recovered in the urine. In a small study comparing a single dose of lamotrigine in subjects with varying degrees of renal impairment with healthy volunteers, the plasma half-life of lamotrigine was approximately twice as long in the subjects with chronic renal failure *[see Clinical Pharmacology (12.3)]*.

Initial doses of lamotrigine should be based on patients' AED regimens; reduced maintenance doses may be effective for patients with significant renal impairment. Few patients with severe renal impairment have been evaluated during chronic treatment with lamotrigine. Because there is inadequate experience in this population, lamotrigine should be used with caution in these patients *[see Dosage and Administration (2.1)]*.

10 OVERDOSAGE

10.1 Human Overdose Experience

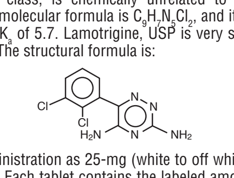
Overdoses involving quantities up to 15 g have been reported for lamotrigine, some of which have been fatal. Overdose has resulted in ataxia, nystagmus, seizures (including tonic-clonic seizures), decreased level of consciousness, coma, and intraventricular conduction delay.

10.2 Management of Overdose

There are no specific antidotes for lamotrigine. 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; usual precautions should be taken to protect the airway. It should be kept in mind that immediate-release lamotrigine is rapidly absorbed *[see Clinical Pharmacology (12.3)]*. 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. A Poison Control Center should be contacted for information on the management of overdosage of lamotrigine.

11 DESCRIPTION

Lamotrigine, USP an AED of the phenyltriazine class, is chemically unrelated to existing AEDs. Lamotrigine's chemical name is 3,5-diamino-6-(2,3-dichlorophenyl)-*as*-triazine, its molecular formula is $C_9H_7N_5Cl_2$, and its molecular weight is 256.09. Lamotrigine, USP is a white to pale cream-colored powder and has a pK_a of 5.7. Lamotrigine, USP is very slightly soluble in water (0.17 mg/mL at 25°C) and slightly soluble in 0.1 M HCl (4.1 mg/mL at 25°C). The structural formula is:



Lamotrigine tablets, USP are supplied for oral administration as 25-mg (white to off white), 100-mg (white to off white), 150-mg (white to off white), and 200-mg (white to off white) tablets. Each tablet contains the labeled amount of lamotrigine, USP and the following inactive ingredients: lactose monohydrate; magnesium stearate; microcrystalline cellulose; povidone; and sodium starch glycolate.

Meets USP Dissolution Test 3

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism(s) by which lamotrigine exerts its anticonvulsant action are unknown. In animal models designed to detect anticonvulsant activity, lamotrigine was effective in preventing seizure spread in the maximum electroshock (MES) and pentylenetetrazol (scMet) tests, and prevented seizures in the visually and electrically evoked after-discharge (EEAD) tests for antiepileptic activity. Lamotrigine also displayed inhibitory properties in the kindling model in rats both during kindling development and in the fully kindled state. The relevance of these models to human epilepsy, however, is not known.

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

Effect of Lamotrigine on N-Methyl d-Aspartate-Receptor-Mediated Activity

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

The mechanisms by which lamotrigine exerts its therapeutic action in bipolar disorder have not been established.

12.2 Pharmacodynamics

Folate Metabolism

In vitro, lamotrigine inhibited dihydrofolate reductase, the enzyme that catalyzes the reduction of dihydrofolate to tetrahydrofolate. Inhibition of this enzyme may interfere with the biosynthesis of nucleic acids and proteins. When oral daily doses of lamotrigine were given to pregnant rats during organogenesis, fetal, placental, and maternal folate concentrations were reduced. Significantly reduced concentrations of folate are associated with teratogenesis *[see Use in Specific Populations (8.1)]*. Folate concentrations were also reduced in male rats given repeated oral doses of lamotrigine. Reduced concentrations were partially returned to normal when supplemented with folinic acid.

Cardiac Electrophysiology

Effect of Lamotrigine: In vitro studies show that lamotrigine exhibits Class IB antiarrhythmic activity at therapeutically relevant concentrations. It inhibits human cardiac sodium channels with rapid onset and offset kinetics and strong voltage dependence, consistent with other Class IB antiarrhythmic agents. At therapeutic doses, lamotrigine did not slow ventricular conduction (widen QRS) in healthy individuals in a thorough QT study; however, in patients with clinically important structural or functional heart disease (i.e., patients with heart failure, valvular heart disease, congenital heart disease, conduction system disease, ventricular arrhythmias, cardiac channelopathies [e.g., Brugada syndrome], clinically important ischemic heart disease, or multiple risk factors for coronary artery disease), lamotrigine could slow ventricular conduction (widen QRS) and induce proarrhythmia, which can lead to sudden death. Elevated heart rates could also increase the risk of ventricular conduction slowing with lamotrigine.

Effect of Lamotrigine Metabolite: In dogs, lamotrigine is extensively metabolized to a 2-N- methyl metabolite. This metabolite causes dose-dependent prolongation of the PR interval, widening of the QRS complex, and, at higher doses, complete AV conduction block. The in vitro electrophysiological effects of this metabolite have not been studied. Similar cardiovascular effects from this metabolite are not anticipated in humans because only trace amounts of the 2-N-methyl metabolite (<0.6% of lamotrigine dose) have been found in human urine *[see Clinical Pharmacology (12.3)]*. However, it is conceivable that plasma concentrations of this metabolite could be increased in patients with a reduced capacity to glucuronidate lamotrigine (e.g., in patients with liver disease, patients taking concomitant medications that inhibit glucuronidation).

Accumulation in Kidneys

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

Melanin Binding

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

12.3 Pharmacokinetics

The pharmacokinetics of lamotrigine have been studied in subjects with epilepsy, healthy young and elderly volunteers, and volunteers with chronic renal failure. Lamotrigine pharmacokinetic parameters for adult and pediatric subjects and healthy normal volunteers are summarized in Tables 14 and 16.

Table 14. Mean Pharmacokinetic Parameters[a] in Healthy Volunteers and Adult Subjects with Epilepsy

Adult Study Population	Number of Subjects	T_{max}: Time of Maximum Plasma Concentration (h)	$t_{1/2}$: Elimination Half-life (h)	CL/F: Apparent Plasma Clearance (mL/min/kg)
Healthy volunteers taking no other medications:				
Single-dose Lamotrigine	179	2.2 (0.25 to 12.0)	32.8 (14.0 to 103.0)	0.44 (0.12 to 1.10)
Multiple-dose Lamotrigine	36	1.7 (0.5 to 4.0)	25.4 (11.6 to 61.6)	0.58 (0.24 to 1.15)
Healthy volunteers taking valproate:				
Single-dose Lamotrigine	6	1.8 (1.0 to 4.0)	48.3 (31.5 to 88.6)	0.30 (0.14 to 0.42)
Multiple-dose Lamotrigine	18	1.9 (0.5 to 3.5)	70.3 (41.9 to 113.5)	0.18 (0.12 to 0.33)
Subjects with epilepsy taking valproate only:				
Single-dose Lamotrigine	4	4.8 (1.8 to 8.4)	58.8 (30.5 to 88.8)	0.28 (0.16 to 0.40)
Subjects with epilepsy taking carbamazepine, phenytoin, phenobarbital, or primidone[b] plus valproate:				
Single-dose Lamotrigine	25	3.8 (1.0 to 10.0)	27.2 (11.2 to 51.6)	0.53 (0.27 to 1.04)
Subjects with epilepsy taking carbamazepine, phenytoin, phenobarbital, or primidone[b]:				
Single-dose Lamotrigine	24	2.3 (0.5 to 5.0)	14.4 (6.4 to 30.4)	1.10 (0.51 to 2.22)
Multiple-dose Lamotrigine	17	2.0 (0.75 to 5.93)	12.6 (7.5 to 23.1)	1.21 (0.66 to 1.82)

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

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

Absorption

Lamotrigine is rapidly and completely absorbed after oral administration with negligible first-pass metabolism (absolute bioavailability is 98%). The bioavailability is not affected by food. Peak plasma concentrations occur anywhere from 1.4 to 4.8 hours following drug administration.

Dose Proportionality

In healthy volunteers not receiving any other medications and given single doses, the plasma concentrations of lamotrigine increased in direct proportion to the dose administered over the range of 50 to 400 mg. In 2 small studies (n = 7 and 8) of patients with epilepsy who were maintained on other AEDs, there also was a linear relationship between dose and lamotrigine plasma concentrations at steady state following doses of 50 to 350 mg twice daily.

Distribution

Estimates of the mean apparent volume of distribution (Vd/F) of lamotrigine following oral administration ranged from 0.9 to 1.3 L/kg. Vd/F is independent of dose and is similar following single and multiple doses in both patients with epilepsy and in healthy volunteers.

Protein Binding

Data from in vitro studies indicate that lamotrigine is approximately 55% bound to human plasma proteins at plasma lamotrigine concentrations from 1 to 10 mcg/mL (10 mcg/mL is 4 to 6 times the trough plasma concentration observed in the controlled efficacy trials). Because lamotrigine is not highly bound to plasma proteins, clinically significant interactions with other drugs through competition for protein binding sites are unlikely. The binding of lamotrigine to plasma proteins did not change in the presence of therapeutic concentrations of phenytoin, phenobarbital, or valproate. Lamotrigine did not displace other AEDs (carbamazepine, phenytoin, phenobarbital) from protein-binding sites.

Metabolism

Lamotrigine is metabolized predominantly by glucuronic acid conjugation; the major metabolite is an inactive 2-N-glucuronide conjugate. After oral administration of 240 mg of ^{14}C-lamotrigine (15 µCi) to 6 healthy volunteers, 94% was recovered in the urine and 2% was recovered in the feces. The radioactivity in the urine consisted of unchanged lamotrigine (10%), the 2-N-glucuronide (76%), a 5-N-glucuronide (10%), a 2-N-methyl metabolite (0.14%), and other unidentified minor metabolites (4%).

Enzyme Induction

The effects of lamotrigine on the induction of specific families of mixed-function oxidase isozymes have not been systematically evaluated.

Following multiple administrations (150 mg twice daily) to normal volunteers taking no other medications, lamotrigine induced its own metabolism, resulting in a 25% decrease in $t_{½}$ and a 37% increase in CL/F at steady state compared with values obtained in the same volunteers following a single dose. Evidence gathered from other sources suggests that self-induction by lamotrigine may not occur when lamotrigine is given as adjunctive therapy in patients receiving enzyme-inducing drugs such as carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir that induce lamotrigine glucuronidation *[see Drug Interactions (7)]*.

Elimination

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

Drug Interactions

The apparent clearance of lamotrigine is affected by the coadministration of certain medications *[see Warnings and Precautions (5.9, 5.13), Drug Interactions (7)]*.

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

Table 15. Summary of Drug Interactions with Lamotrigine

Drug	Drug Plasma Concentration with Adjunctive Lamotrigine[a]	Lamotrigine Plasma Concentration with Adjunctive Drugs[b]
Oral contraceptives (e.g., ethinylestradiol/levonorgestrel)[c]	↔[d]	↓
Aripiprazole	Not assessed	↔[e]
Atazanavir/ritonavir	↔[f]	↓
Bupropion	Not assessed	↔
Carbamazepine	↔	↓
Carbamazepine epoxide[g]	?	
Felbamate	Not assessed	↔
Gabapentin	Not assessed	↔
Lacosamide	Not assessed	↔
Levetiracetam	↔	↔
Lithium	↔	Not assessed
Lopinavir/ritonavir	↔[e]	↓
Olanzapine	↔	↔[e]
Oxcarbazepine	↔	↔
10-Monohydroxy oxcarbazepine metabolite[h]	↔	
Perampanel	Not assessed	↔[e]
Phenobarbital/primidone	↔	↓
Phenytoin	↔	↓
Pregabalin	↔	↔
Rifampin	Not assessed	↓
Risperidone	↔	Not assessed
9-Hydroxyrisperidone[i]	↔	
Topiramate	↔[j]	↔
Valproate	↓	↑
Valproate + phenytoin and/or carbamazepine	Not assessed	↔
Zonisamide	Not assessed	↔

[a] From adjunctive clinical trials and volunteer trials.
[b] Net effects were estimated by comparing the mean clearance values obtained in adjunctive clinical trials and volunteer trials.
[c] The effect of other hormonal contraceptive preparations or hormone replacement therapy on the pharmacokinetics of lamotrigine has not been systematically evaluated in clinical trials, although the effect may be similar to that seen with the ethinylestradiol/levonorgestrel combinations.
[d] Modest decrease in levonorgestrel.
[e] Slight decrease, not expected to be clinically meaningful.
[f] Compared with historical controls.
[g] Not administered, but an active metabolite of carbamazepine.
[h] Not administered, but an active metabolite of oxcarbazepine.
[i] Not administered, but an active metabolite of risperidone.
[j] Slight increase, not expected to be clinically meaningful.
↔ = No significant effect.
? = Conflicting data.

Estrogen-Containing Oral Contraceptives

In 16 female volunteers, an oral contraceptive preparation containing 30 mcg ethinylestradiol and 150 mcg levonorgestrel increased the apparent clearance of lamotrigine (300 mg/day) by approximately 2-fold with mean decreases in AUC of 52% and in C_{max} of 39%. In this study, trough serum lamotrigine concentrations gradually increased and were approximately 2-fold higher on average at the end of the week of the inactive hormone preparation compared with trough lamotrigine concentrations at the end of the active hormone cycle.

Gradual transient increases in lamotrigine plasma levels (approximate 2-fold increase) occurred during the week of inactive hormone preparation (pill-free week) for women not also taking a drug that increased the clearance of lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir that induce lamotrigine glucuronidation) *[see Drug Interactions (7)]*. The increase in lamotrigine plasma levels will be greater if the dose of lamotrigine is increased in the few days before or during the pill-free week. Increases in lamotrigine plasma levels could result in dose-dependent adverse reactions.

In the same study, coadministration of lamotrigine (300 mg/day) in 16 female volunteers did not affect the pharmacokinetics of the ethinylestradiol component of the oral contraceptive preparation. There were mean decreases in the AUC and C_{max} of the levonorgestrel component of 19% and 12%, respectively. Measurement of serum progesterone indicated that there was no hormonal evidence of ovulation in any of the 16 volunteers, although measurement of serum FSH, LH, and estradiol indicated that there was some loss of suppression of the hypothalamic-pituitary-ovarian axis.

The effects of doses of lamotrigine other than 300 mg/day have not been systematically evaluated in controlled clinical trials.

The clinical significance of the observed hormonal changes on ovulatory activity is unknown. However, the possibility of decreased contraceptive efficacy in some patients cannot be excluded. Therefore, patients should be instructed to promptly report changes in their menstrual pattern (e.g., break-through bleeding).

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

Other Hormonal Contraceptives or Hormone Replacement Therapy

The effect of other hormonal contraceptive preparations or hormone replacement therapy on the pharmacokinetics of lamotrigine has not been systematically evaluated. It has been reported that ethinylestradiol, not progestogens, increased the clearance of lamotrigine up to 2-fold, and the progestin-only pills had no effect on lamotrigine plasma levels. Therefore, adjustments to the dosage of lamotrigine in the presence of progestogens alone will likely not be needed.

Aripiprazole

In 18 patients with bipolar disorder on a stable regimen of 100 to 400 mg/day of lamotrigine, the lamotrigine AUC and C_{max} were reduced by approximately 10% in patients who received aripiprazole 10 to 30 mg/day for 7 days, followed by 30 mg/day for an additional 7 days. This reduction in lamotrigine exposure is not considered clinically meaningful.

Atazanavir/Ritonavir

In a study in healthy volunteers, daily doses of atazanavir/ritonavir (300 mg/100 mg) reduced the plasma AUC and C_{max} of lamotrigine (single 100-mg dose) by an average of 32% and 6%, respectively, and shortened the elimination half-lives by 27%. In the presence of atazanavir/ritonavir (300 mg/100 mg), the metabolite-to-lamotrigine ratio was increased from 0.45 to 0.71 consistent with induction of glucuronidation. The pharmacokinetics of atazanavir/ritonavir were similar in the presence of concomitant lamotrigine to the historical data of the pharmacokinetics in the absence of lamotrigine.

Bupropion

The pharmacokinetics of a 100-mg single dose of lamotrigine in healthy volunteers (n = 12) were not changed by coadministration of bupropion sustained-release formulation (150 mg twice daily) starting 11 days before lamotrigine.

Carbamazepine

Lamotrigine has no appreciable effect on steady-state carbamazepine plasma concentration. Limited clinical data suggest there is a higher incidence of dizziness, diplopia, ataxia, and blurred vision in patients receiving carbamazepine with lamotrigine than in patients receiving other AEDs with lamotrigine *[see Adverse Reactions (6.1)]*. The mechanism of this interaction is unclear. The effect of lamotrigine on plasma concentrations of carbamazepine-epoxide is unclear. In a small subset of patients (n = 7) studied in a placebo-controlled trial, lamotrigine had no effect on carbamazepine-epoxide plasma concentrations, but in a small, uncontrolled study (n = 9), carbamazepine-epoxide levels increased.

The addition of carbamazepine decreases lamotrigine steady-state concentrations by approximately 40%.

Felbamate

In a trial in 21 healthy volunteers, coadministration of felbamate (1,200 mg twice daily) with lamotrigine (100 mg twice daily for 10 days) appeared to have no clinically relevant effects on the pharmacokinetics of lamotrigine.

Folate Inhibitors

Lamotrigine is a weak inhibitor of dihydrofolate reductase. Prescribers should be aware of this action when prescribing other medications that inhibit folate metabolism.

Gabapentin

Based on a retrospective analysis of plasma levels in 34 subjects who received lamotrigine both with and without gabapentin, gabapentin does not appear to change the apparent clearance of lamotrigine.

Lacosamide

Plasma concentrations of lamotrigine were not affected by concomitant lacosamide (200, 400, or 600 mg/day) in placebo-controlled clinical trials in patients with partial-onset seizures.

Levetiracetam

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

Lithium

The pharmacokinetics of lithium were not altered in healthy subjects (n = 20) by coadministration of lamotrigine (100 mg/day) for 6 days.

Lopinavir/Ritonavir

The addition of lopinavir (400 mg twice daily)/ritonavir (100 mg twice daily) decreased the AUC, C_{max}, and elimination half-life of lamotrigine by approximately 50% to 55.4% in 18 healthy subjects. The pharmacokinetics of lopinavir/ritonavir were similar with concomitant lamotrigine, compared with that in historical controls.

Olanzapine

The AUC and C_{max} of olanzapine were similar following the addition of olanzapine (15 mg once daily) to lamotrigine (200 mg once daily) in healthy male volunteers (n = 16) compared with the AUC and C_{max} in healthy male volunteers receiving olanzapine alone (n = 16).

In the same trial, the AUC and C_{max} of lamotrigine were reduced on average by 24% and 20%, respectively, following the addition of olanzapine to lamotrigine in healthy male volunteers compared with those receiving lamotrigine alone. This reduction in lamotrigine plasma concentrations is not expected to be clinically meaningful.

Oxcarbazepine

The AUC and C_{max} of oxcarbazepine and its active 10-monohydroxy oxcarbazepine metabolite were not significantly different following the addition of oxcarbazepine (600 mg twice daily) to lamotrigine (200 mg once daily) in healthy male volunteers (n = 13) compared with healthy male volunteers receiving oxcarbazepine alone (n = 13).

In the same trial, the AUC and C_{max} of lamotrigine were similar following the addition of oxcarbazepine (600 mg twice daily) to lamotrigine in healthy male volunteers compared with those receiving lamotrigine alone. Limited clinical data suggest a higher incidence of headache, dizziness, nausea, and somnolence with coadministration of lamotrigine and oxcarbazepine compared with lamotrigine alone or oxcarbazepine alone.

Perampanel

In a pooled analysis of data from 3 placebo-controlled clinical trials investigating adjunctive perampanel in patients with partial-onset and primary generalized tonic-clonic seizures, the highest perampanel dose evaluated (12 mg/day) increased lamotrigine clearance by <10%. An effect of this magnitude is not considered to be clinically relevant.

Phenobarbital, Primidone

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

Phenytoin

Lamotrigine has no appreciable effect on steady-state phenytoin plasma concentrations in patients with epilepsy. The addition of phenytoin decreases lamotrigine steady-state concentrations by approximately 40%.

Pregabalin

Steady-state trough plasma concentrations of lamotrigine were not affected by concomitant pregabalin (200 mg 3 times daily) administration. There are no pharmacokinetic interactions between lamotrigine and pregabalin.

Rifampin

In 10 male volunteers, rifampin (600 mg/day for 5 days) significantly increased the apparent clearance of a single 25-mg dose of lamotrigine by approximately 2-fold (AUC decreased by approximately 40%).

Risperidone

In a 14 healthy volunteers study, multiple oral doses of lamotrigine 400 mg daily had no clinically significant effect on the single-dose pharmacokinetics of risperidone 2 mg and its active metabolite 9-OH risperidone. Following the coadministration of risperidone 2 mg with lamotrigine, 12 of the 14 volunteers reported somnolence compared with 1 out of 20 when risperidone was given alone, and none when lamotrigine was administered alone.

Topiramate

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

Valproate

When lamotrigine was administered to healthy volunteers (n = 18) receiving valproate, the trough steady-state valproate plasma concentrations decreased by an average of 25% over a 3-week period, and then stabilized. However, adding lamotrigine to the existing therapy did not cause a change in valproate plasma concentrations in either adult or pediatric patients in controlled clinical trials.

The addition of valproate increased lamotrigine steady-state concentrations in normal volunteers by slightly more than 2-fold. In 1 trial, maximal inhibition of lamotrigine clearance was reached at valproate doses between 250 and 500 mg/day and did not increase as the valproate dose was further increased.

Zonisamide

In a study in 18 patients with epilepsy, coadministration of zonisamide (200 to 400 mg/day) with lamotrigine (150 to 500 mg/day for 35 days) had no significant effect on the pharmacokinetics of lamotrigine.

Known Inducers or Inhibitors of Glucuronidation

Drugs other than those listed above have not been systematically evaluated in combination with lamotrigine. Since lamotrigine is metabolized predominately by glucuronic acid conjugation, drugs that are known to induce or inhibit glucuronidation may affect the apparent clearance of lamotrigine and doses of lamotrigine may require adjustment based on clinical response.

Other

In vitro assessment of the inhibitory effect of lamotrigine at OCT2 demonstrate that lamotrigine, but not the N(2)-glucuronide metabolite, is an inhibitor of OCT2 at potentially clinically relevant concentrations, with IC_{50} value of 53.8 µM *[see Drug Interactions (7)]*.

Results of in vitro experiments suggest that clearance of lamotrigine is unlikely to be reduced by concomitant administration of amitriptyline, clonazepam, clozapine, fluoxetine, haloperidol, lorazepam, phenelzine, sertraline, or trazodone.

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

Specific Populations

Patients with Renal Impairment: Twelve volunteers with chronic renal failure (mean creatinine clearance: 13 mL/min, range: 6 to 23) and another 6 individuals undergoing hemodialysis were each given a single 100-mg dose of lamotrigine. The mean plasma half-lives determined in the study were 42.9 hours (chronic renal failure), 13.0 hours (during hemodialysis), and 57.4 hours (between hemodialysis) compared with 26.2 hours in healthy volunteers. On average, approximately 20% (range: 5.6 to 35.1) of the amount of lamotrigine present in the body was eliminated by hemodialysis during a 4-hour session *[see Dosage and Administration (2.1)]*.

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

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

Population pharmacokinetic analyses involving subjects aged 2 to 18 years demonstrated that lamotrigine clearance was influenced predominantly by total body weight and concurrent AED therapy. The oral clearance of lamotrigine was higher, on a body weight basis, in pediatric patients than in adults. Weight-normalized lamotrigine clearance was higher in those subjects weighing <30 kg compared with those weighing >30 kg. Accordingly, patients weighing <30 kg may need an increase of as much as 50% in maintenance doses, based on clinical response, as compared with subjects weighing >30 kg being administered the same AEDs *[see Dosage and Administration (2.2)]*. These analyses also revealed that, after accounting for body weight, lamotrigine clearance was not significantly influenced by age. Thus, the same weight-adjusted doses should be administered to children irrespective of differences in age. Concomitant AEDs which influence lamotrigine clearance in adults were found to have similar effects in children.

Table 16. Mean Pharmacokinetic Parameters in Pediatric Subjects with Epilepsy

Pediatric Study Population	Number of Subjects	T_{max} (h)	$t_{1/2}$ (h)	CL/F (mL/min/kg)
Ages 10 months to 5.3 years				
Subjects taking carbamazepine, phenytoin, phenobarbital, or primidone[a]	10	3.0 (1.0 to 5.9)	7.7 (5.7 to 11.4)	3.62 (2.44 to 5.28)
Subjects taking antiepileptic drugs with no known effect on the apparent clearance of lamotrigine	7	5.2 (2.9 to 6.1)	19.0 (12.9 to 27.1)	1.2 (0.75 to 2.42)
Subjects taking valproate only	8	2.9 (1.0 to 6.0)	44.9 (29.5 to 52.5)	0.47 (0.23 to 0.77)
Ages 5 to 11 years				
Subjects taking carbamazepine, phenytoin, phenobarbital, or primidone[a]	7	1.6 (1.0 to 3.0)	7.0 (3.8 to 9.8)	2.54 (1.35 to 5.58)
Subjects taking carbamazepine, phenytoin, phenobarbital, or primidone[a] plus valproate	8	3.3 (1.0 to 6.4)	19.1 (7.0 to 31.2)	0.89 (0.39 to 1.93)
Subjects taking valproate only[b]	3	4.5 (3.0 to 6.0)	65.8 (50.7 to 73.7)	0.24 (0.21 to 0.26)
Ages 13 to 18 years				
Subjects taking carbamazepine, phenytoin, phenobarbital, or primidone[a]	11	—[c]	—[c]	1.3
Subjects taking carbamazepine, phenytoin, phenobarbital, or primidone[a] plus valproate	8	—[c]	—[c]	0.5
Subjects taking valproate only	4	—[c]	—[c]	0.3

[a] Carbamazepine, phenytoin, phenobarbital, and primidone have been shown to increase the apparent clearance of lamotrigine. Estrogen-containing oral contraceptives, rifampin, and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir have also been shown to increase the apparent clearance of lamotrigine *[see Drug Interactions (7)]*.
[b] Two subjects were included in the calculation for mean T_{max}.
[c] Parameter not estimated.

Geriatric Patients: The pharmacokinetics of lamotrigine following a single 150-mg dose of lamotrigine were evaluated in 12 elderly volunteers between the ages of 65 and 76 years (mean creatinine clearance = 61 mL/min, range: 33 to 108 mL/min). The mean half-life of lamotrigine in these subjects was 31.2 hours (range: 24.5 to 43.4 hours), and the mean clearance was 0.40 mL/min/kg (range: 0.26 to 0.48 mL/min/kg).

Male and Female Patients: The clearance of lamotrigine is not affected by gender. However, during dose escalation of lamotrigine in 1 clinical trial in patients with epilepsy on a stable dose of valproate (n = 77), mean trough lamotrigine concentrations unadjusted for weight were 24% to 45% higher (0.3 to 1.7 mcg/mL) in females than in males.

Racial or Ethnic Groups: The apparent oral clearance of lamotrigine was 25% lower in non-Caucasians than Caucasians.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenicity was seen in mice or rats following oral administration of lamotrigine for up to 2 years at doses up to 30 mg/kg/day and 10 to 15 mg/kg/day, respectively. The highest doses tested are less than the human dose of 400 mg/day on a body surface area (mg/m^2) basis.

Lamotrigine was negative in in vitro gene mutation (Ames and mouse lymphoma *tk*) assays and in clastogenicity (in vitro human lymphocyte and in vivo rat bone marrow) assays.

No evidence of impaired fertility was detected in rats given oral doses of lamotrigine up to 20 mg/kg/day. The highest dose tested is less than the human dose of 400 mg/day on a mg/m^2 basis.

14 CLINICAL STUDIES

14.1 Epilepsy

Monotherapy with Lamotrigine in Adults with Partial-Onset Seizures Already Receiving Treatment with Carbamazepine, Phenytoin, Phenobarbital, or Primidone as the Single Antiepileptic Drug

The effectiveness of monotherapy with lamotrigine was established in a multicenter, double-blind clinical trial enrolling 156 adult outpatients with partial-onset seizures. The patients experienced at least 4 simple partial-onset, complex partial-onset, and/or secondarily generalized seizures during each of 2 consecutive 4-week periods while receiving carbamazepine or phenytoin monotherapy during baseline. Lamotrigine (target dose of 500 mg/day) or valproate (1,000 mg/day) was added to either carbamazepine or phenytoin monotherapy over a 4-week period. Patients were then converted to monotherapy with lamotrigine or valproate during the next 4 weeks, then continued on monotherapy for an additional 12-week period.

Trial endpoints were completion of all weeks of trial treatment or meeting an escape criterion. Criteria for escape relative to baseline were: (1) doubling of average monthly seizure count, (2) doubling of highest consecutive 2-day seizure frequency, (3) emergence of a new seizure type (defined as a seizure that did not occur during the 8-week baseline) that is more severe than seizure types that occur during study treatment, or (4) clinically significant prolongation of generalized tonic-clonic seizures. The primary efficacy variable was the proportion of patients in each treatment group who met escape criteria.

The percentages of patients who met escape criteria were 42% (32/76) in the group receiving lamotrigine and 69% (55/80) in the valproate group. The difference in the percentage of patients meeting escape criteria was statistically significant (P = 0.0012) in favor of lamotrigine. No differences in efficacy based on age, sex, or race were detected.

Patients in the control group were intentionally treated with a relatively low dose of valproate; as such, the sole objective of this trial was to demonstrate the effectiveness and safety of monotherapy with lamotrigine, and cannot be interpreted to imply the superiority of lamotrigine to an adequate dose of valproate.

Adjunctive Therapy with Lamotrigine in Adults with Partial-Onset Seizures

The effectiveness of lamotrigine as adjunctive therapy (added to other AEDs) was initially established in 3 pivotal, multicenter, placebo-controlled, double-blind clinical trials in 355 adults with refractory partial-onset seizures. The patients had a history of at least 4 partial-onset seizures per month in spite of receiving 1 or more AEDs at therapeutic concentrations and in 2 of the trials were observed on their established AED regimen during baselines that varied between 8 to 12 weeks. In the third trial, patients were not observed in a prospective baseline. In patients continuing to have at least 4 seizures per month during the baseline, lamotrigine or placebo was then added to the existing therapy. In all 3 trials, change from baseline in seizure frequency was the primary measure of effectiveness. The results given below are for all partial-onset seizures in the intent-to-treat population (all patients who received at least 1 dose of treatment) in each trial, unless otherwise indicated. The median seizure frequency at baseline was 3 per week while the mean at baseline was 6.6 per week for all patients enrolled in efficacy trials.

One trial (n = 216) was a double-blind, placebo-controlled, parallel trial consisting of a 24-week treatment period. Patients could not be on more than 2 other anticonvulsants and valproate was not allowed. Patients were randomized to receive placebo, a target dose of 300 mg/day of lamotrigine, or a target dose of 500 mg/day of lamotrigine. The median reductions in the frequency of all partial-onset seizures relative to baseline were 8% in patients receiving placebo, 20% in patients receiving 300 mg/day of lamotrigine, and 36% in patients receiving 500 mg/day of lamotrigine. The seizure frequency reduction was statistically significant in the 500-mg/day group compared with the placebo group, but not in the 300-mg/day group.

A second trial (n = 98) was a double-blind, placebo-controlled, randomized, crossover trial consisting of two 14-week treatment periods (the last 2 weeks of which consisted of dose tapering) separated by a 4-week washout period. Patients could not be on more than 2 other anticonvulsants and valproate was not allowed. The target dose of lamotrigine was 400 mg/day. When the first 12 weeks of the treatment periods were analyzed, the median change in seizure frequency was a 25% reduction on lamotrigine compared with placebo (P<0.001).

The third trial (n = 41) was a double-blind, placebo-controlled, crossover trial consisting of two 12-week treatment periods separated by a 4-week washout period. Patients could not be on more than 2 other anticonvulsants. Thirteen patients were on concomitant valproate; these patients received 150 mg/day of lamotrigine. The 28 other patients had a target dose of 300 mg/day of lamotrigine. The median change in seizure frequency was a 26% reduction on lamotrigine compared with placebo (P<0.01).

No differences in efficacy based on age, sex, or race, as measured by change in seizure frequency, were detected.

Adjunctive Therapy with Lamotrigine in Pediatric Patients with Partial-Onset Seizures

The effectiveness of lamotrigine as adjunctive therapy in pediatric patients with partial-onset seizures was established in a multicenter, double-blind, placebo-controlled trial in 199 patients aged 2 to 16 years (n = 98 on lamotrigine, n = 101 on placebo). Following an 8-week baseline phase, patients were randomized to 18 weeks of treatment with lamotrigine or placebo added to their current AED regimen of up to 2 drugs. Patients were dosed based on body weight and valproate use. Target doses were designed to approximate 5 mg/kg/day for patients taking valproate (maximum dose: 250 mg/day) and 15 mg/kg/day for the patients not taking valproate (maximum dose: 750 mg/day). The primary efficacy endpoint was percentage change from baseline in all partial-onset seizures. For the intent-to-treat population, the median reduction of all partial-onset seizures was 36% in patients treated with lamotrigine and 7% on placebo, a difference that was statistically significant (P<0.01).

Adjunctive Therapy with Lamotrigine in Pediatric and Adult Patients with Lennox-Gastaut Syndrome

The effectiveness of lamotrigine as adjunctive therapy in patients with Lennox-Gastaut syndrome was established in a multicenter, double-blind, placebo-controlled trial in 169 patients aged 3 to 25 years (n = 79 on lamotrigine, n = 90 on placebo). Following a 4-week, single-blind, placebo phase, patients were randomized to 16 weeks of treatment with lamotrigine or placebo added to their current AED regimen of up to 3 drugs. Patients were dosed on a fixed-dose regimen based on body weight and valproate use. Target doses were designed to approximate 5 mg/kg/day for patients taking valproate (maximum dose: 200 mg/day) and 15 mg/kg/day for patients not taking valproate (maximum dose: 400 mg/day). The primary efficacy endpoint was percentage change from baseline in major motor seizures (atonic, tonic, major myoclonic, and tonic-clonic seizures). For the intent-to-treat population, the median reduction of major motor seizures was 32% in patients treated with lamotrigine and 9% on placebo, a difference that was statistically significant (P<0.05). Drop attacks were significantly reduced by lamotrigine (34%) compared with placebo (9%), as were tonic-clonic seizures (36% reduction versus 10% increase for lamotrigine and placebo, respectively).

Adjunctive Therapy with Lamotrigine in Pediatric and Adult Patients with Primary Generalized Tonic-Clonic Seizures

The effectiveness of lamotrigine as adjunctive therapy in patients with PGTC seizures was established in a multicenter, double-blind, placebo-controlled trial in 117 pediatric and adult patients aged 2 years and older (n = 58 on lamotrigine, n = 59 on placebo). Patients with at least 3 PGTC seizures during an 8-week baseline phase were randomized to 19 to 24 weeks of treatment with lamotrigine or placebo added to their current AED regimen of up to 2 drugs. Patients were dosed on a fixed-dose regimen, with target doses ranging from 3 to 12 mg/kg/day for pediatric patients and from 200 to 400 mg/day for adult patients based on concomitant AEDs.

The primary efficacy endpoint was percentage change from baseline in PGTC seizures. For the intent-to-treat population, the median percent reduction in PGTC seizures was 66% in patients treated with lamotrigine and 34% on placebo, a difference that was statistically significant (P = 0.006).

14.2 Bipolar Disorder

Adults

The effectiveness of lamotrigine in the maintenance treatment of bipolar I disorder was established in 2 multicenter, double-blind, placebo-controlled trials in adult patients (aged 18 to 82 years) who met DSM-IV criteria for bipolar I disorder. Trial 1 enrolled patients with a current or recent (within 60 days) depressive episode as defined by DSM-IV and Trial 2 included patients with a current or recent (within 60 days) episode of mania or hypomania as defined by DSM-IV. Both trials included a cohort of patients (30% of 404 subjects in Trial 1 and 28% of 171 patients in Trial 2) with rapid cycling bipolar disorder (4 to 6 episodes per year).

In both trials, patients were titrated to a target dose of 200 mg of lamotrigine as add-on therapy or as monotherapy with gradual withdrawal of any psychotropic medications during an 8- to 16-week open-label period. Overall 81% of 1,305 patients participating in the open-label period were receiving 1 or more other psychotropic medications, including benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), atypical antipsychotics (including olanzapine), valproate, or lithium, during titration of lamotrigine. Patients with a CGI-severity score of 3 or less maintained for at least 4 continuous weeks, including at least the final week on monotherapy with lamotrigine, were randomized to a placebo-controlled double-blind treatment period for up to 18 months. The primary endpoint was TIME (time to intervention for a mood episode or one that was emerging, time to discontinuation for either an adverse event that was judged to be related to bipolar disorder, or for lack of efficacy). The mood episode could be depression, mania, hypomania, or a mixed episode.

In Trial 1, patients received double-blind monotherapy with lamotrigine 50 mg/day (n = 50), lamotrigine 200 mg/day (n = 124), lamotrigine 400 mg/day (n = 47), or placebo (n = 121). Lamotrigine (200- and 400-mg/day treatment groups combined) was superior to placebo in delaying the time to occurrence of a mood episode (Figure 1). Separate analyses of the 200- and 400-mg/day dose groups revealed no added benefit from the higher dose.

In Trial 2, patients received double-blind monotherapy with lamotrigine (100 to 400 mg/day, n = 59), or placebo (n = 70). Lamotrigine was superior to placebo in delaying time to occurrence of a mood episode (Figure 2). The mean dose of lamotrigine was about 211 mg/day.

Although these trials were not designed to separately evaluate time to the occurrence of depression or mania, a combined analysis for the 2 trials revealed a statistically significant benefit for lamotrigine over placebo in delaying the time to occurrence of both depression and mania, although the finding was more robust for depression.

Figure 1: Kaplan-Meier Estimation of Cumulative Proportion of Patients with Mood Episode (Trial 1)

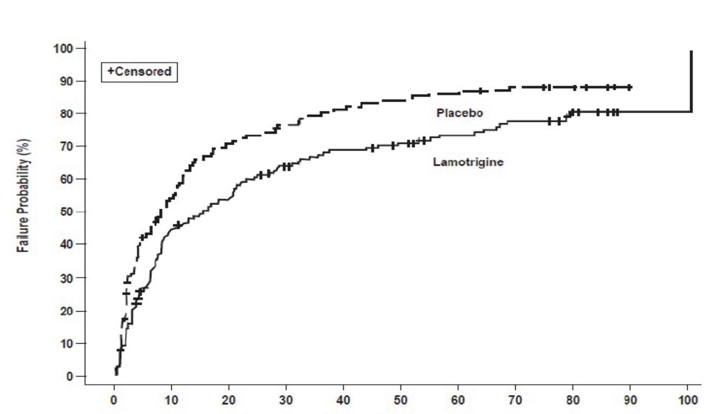
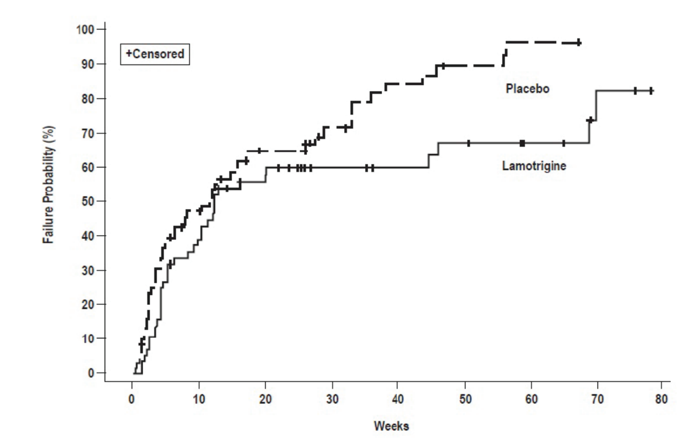


Figure 2: Kaplan-Meier Estimation of Cumulative Proportion of Patients with Mood Episode (Trial 2)



16 HOW SUPPLIED/STORAGE AND HANDLING

Lamotrigine Tablets, USP 25-mg

White to off white, round shape, flat face beveled edge, uncoated tablets debossed with "45" on one side and break line on other side.

Bottle of 30	NDC-13668-045-30
Bottle of 60	NDC-13668-045-60
Bottle of 100	NDC-13668-045-01
Bottle of 500	NDC-13668-045-05
Bottle of 6600	NDC-13668-045-66
10 x 10 unit dose	NDC-13668-045-74

Lamotrigine Tablets, USP 100-mg

White to off white, round shape, flat face beveled edge, uncoated tablets debossed with "1047" on one side and break line on other side.

Bottle of 30	NDC-13668-047-30
Bottle of 60	NDC-13668-047-60
Bottle of 100	NDC-13668-047-01
Bottle of 500	NDC-13668-047-05
Bottle of 2500	NDC-13668-047-31
10 x 10 unit dose	NDC-13668-047-74

Lamotrigine Tablets, USP 150-mg

White to off white, round shape, flat face beveled edge, uncoated tablets debossed with "1048" on one side and break line on other side.

Bottle of 30	NDC-13668-048-30
Bottle of 60	NDC-13668-048-60
Bottle of 100	NDC-13668-048-01
Bottle of 500	NDC-13668-048-05
Bottle of 1600	NDC-13668-048-16
9 x 10 unit dose	NDC-13668-048-64

Lamotrigine Tablets, USP 200-mg

White to off white, round shape, flat face beveled edge, uncoated tablets debossed with "1049" on one side and break line on other side.

Bottle of 30	NDC-13668-049-30
Bottle of 60	NDC-13668-049-60
Bottle of 100	NDC-13668-049-01
Bottle of 500	NDC-13668-049-05
Bottle of 1300	NDC-13668-049-13
9 x 10 unit dose	NDC-13668-049-64

Lamotrigine Tablets, USP Starter Kit for Patients Not Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate (Orange Kit).

25-mg, white to off white, round shape, flat face beveled edge, uncoated tablets debossed with "45" on one side and break line on other side.

100-mg, white to off white, round shape, flat face beveled edge, uncoated tablets debossed with "1047" on one side and break line on other side.

Blister pack of 42, 25-mg tablets and 7, 100-mg tablets NDC-13668-266-99

Lamotrigine Tablets, USP Starter Kit for Patients Taking Carbamazepine, Phenytoin, Phenobarbital, or Primidone and Not Taking Valproate (Green Kit).

25-mg, white to off white, round shape, flat face beveled edge, uncoated tablets debossed with "45" on one side and break line on other side.

100-mg, white to off white, round shape, flat face beveled edge, uncoated tablets debossed with "1047" on one side and break line on other side.

Blister pack of 84, 25-mg tablets and 14, 100-mg tablets NDC-13668-266-28

Lamotrigine Tablets, USP Starter Kit for Patients Taking Valproate (Blue Kit).

25-mg, white to off white, round shape, flat face beveled edge, uncoated tablets debossed with "45" on one side and break line on other side.

Blister pack of 35 tablets NDC-13668-045-29

Storage

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Rash

Prior to initiation of treatment with lamotrigine, inform patients that a rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy) may herald a serious medical event and instruct them to report any such occurrence to their healthcare providers immediately.

Hemophagocytic Lymphohistiocytosis

Prior to initiation of treatment with lamotrigine, inform patients that excessive immune activation may occur with lamotrigine and that they should report signs or symptoms such as fever, rash, or lymphadenopathy to a healthcare provider immediately.

Multiorgan Hypersensitivity Reactions, Blood Dyscrasias, and Organ Failure

Inform patients that multiorgan hypersensitivity reactions and acute multiorgan failure may occur with lamotrigine. Isolated organ failure or isolated blood dyscrasias without evidence of multiorgan hypersensitivity may also occur. Instruct patients to contact their healthcare providers immediately if they experience any signs or symptoms of these conditions *[see Warnings and Precautions (5.3, 5.5)]*.

Cardiac Rhythm and Conduction Abnormalities

Inform patients that, due to its mechanism of action, lamotrigine could lead to irregular or slowed heart rhythm. This risk is increased in patients with underlying cardiac disease or heart conduction problems or who are taking other medications that affect heart conduction. Patients should be made aware of and report cardiac signs or symptoms to their healthcare provider right away. Patients who develop syncope should lie down with raised legs and contact their healthcare provider *[see Warnings and Precautions (5.4)]*.

Suicidal Thinking and Behavior

Inform patients, their caregivers, and families that AEDs, including lamotrigine, may increase the risk of suicidal thoughts and behavior. Instruct them to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts or behavior or thoughts about self-harm. Instruct them to immediately report behaviors of concern to their healthcare providers.

Worsening of Seizures

Instruct patients to notify their healthcare providers if worsening of seizure control occurs.

Central Nervous System Adverse Effects

Inform patients that lamotrigine may cause dizziness, somnolence, and other symptoms and signs of central nervous system depression. Accordingly, instruct them neither to drive a car nor to operate other complex machinery until they have gained sufficient experience on lamotrigine to gauge whether or not it adversely affects their mental and/or motor performance.

Pregnancy and Nursing

Instruct patients to notify their healthcare providers if they become pregnant or intend to become pregnant during therapy and if they intend to breastfeed or are breastfeeding an infant.

Encourage patients to enroll in the NAAED Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll-free number 1-888-233-2334 *[see Use in Specific Populations (8.1)]*.

Inform patients who intend to breastfeed that lamotrigine is present in breast milk and advise them to monitor their child for potential adverse effects of this drug. Discuss the benefits and risks of continuing breastfeeding.

Oral Contraceptive Use

Instruct women to notify their healthcare providers if they plan to start or stop use of oral contraceptives or other female hormonal preparations. Starting estrogen-containing oral contraceptives may significantly decrease lamotrigine plasma levels and stopping estrogen-containing oral contraceptives (including the pill-free week) may significantly increase lamotrigine plasma levels *[see Warnings and Precautions (5.9), Clinical Pharmacology (12.3)]*. Also instruct women to promptly notify their healthcare providers if they experience adverse reactions or changes in menstrual pattern (e.g., break-through bleeding) while receiving lamotrigine in combination with these medications.

Discontinuing Lamotrigine

Instruct patients to notify their healthcare providers if they stop taking lamotrigine for any reason and not to resume lamotrigine without consulting their healthcare providers.

Aseptic Meningitis

Inform patients that lamotrigine may cause aseptic meningitis. Instruct them to notify their healthcare providers immediately if they develop signs and symptoms of meningitis such as headache, fever, nausea, vomiting, stiff neck, rash, abnormal sensitivity to light, myalgia, chills, confusion, or drowsiness while taking lamotrigine.

Potential Medication Errors

To avoid a medication error of using the wrong drug or formulation, strongly advise patients to visually inspect their tablets to verify that they are lamotrigine, as well as the correct formulation of lamotrigine, each time they fill their prescription *[see Dosage Forms and Strengths (3.1), How Supplied/Storage and Handling (16)]*. Refer the patient to the Medication Guide that provides depictions of the lamotrigine tablets.

Dispense with Medication Guide available at: https://torrentpharma.com/pi/usa/products/

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Manufactured for:
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