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

LAMICTAL XR (lamotrigine) Extended-Release Tablets
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, 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 (5.1):

- **coadministration with valproate**
- **exceeding recommended initial dose of LAMICTAL XR**
- **exceeding recommended dose escalation of LAMICTAL XR**

Benign rashes are also caused by lamotrigine; however, it is not possible to predict which rashes will prove to be serious or life-threatening. LAMICTAL XR should be discontinued at the first sign of rash unless the rash is clearly not drug-related. (5.1)

----------RECENT MAJOR CHANGES ----------

Indications and Usage (1)	January/2010
Dosage and Administration (2.2)	January/2010

---------- INDICATIONS AND USAGE----------

LAMICTAL XR is an antiepileptic drug (AED) indicated as adjunctive therapy for primary generalized tonic-clonic (PGTC) seizures and partial onset seizures with or without secondary generalization in patients ≥13 years of age. (1.1)

----------DOSAGE AND ADMINISTRATION----------

- Doses are administered once daily. Dose escalation and maintenance doses are based on concomitant medications. (2.1, 2.2)
- To avoid an increased risk of rash, the recommended initial dose and subsequent dose escalations should not be exceeded. LAMICTAL XR Patient Titration Kits are available for the first 5 weeks of treatment. (2.1, 16)
- For patients being converted from immediate-release lamotrigine to LAMICTAL XR, the initial dose of LAMICTAL XR should match the total daily dose of the immediate-release lamotrigine. Patients should be closely monitored for seizure control after conversion to LAMICTAL XR. (2.3)
- Do not restart LAMICTAL XR in patients who discontinued due to rash unless the potential benefits clearly outweigh the risks. (2.1, 5.1)
- Adjustments to maintenance doses will in most cases be required in patients starting or stopping estrogen-containing oral contraceptives. (2.1, 5.7)
- LAMICTAL XR should be discontinued over a period of at least 2 weeks (approximately 50% reduction per week). (2.1, 5.8)

---------- DOSAGE FORMS AND STRENGTHS----------

Extended-Release Tablets**:** 25 mg, 50 mg, 100 mg, 200 mg, and 300 mg. (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, may result. (Boxed Warning, 5.1)
- Hypersensitivity reaction may be fatal or life-threatening. Early signs of hypersensitivity (e.g., fever, lymphadenopathy) may present without rash; if signs present, patient should be evaluated immediately.
- LAMICTAL XR should be discontinued if alternate etiology for hypersensitivity signs is not found. (5.2)
- Acute multiorgan failure has resulted (some cases fatal). (5.3)
- Blood dyscrasias (e.g., neutropenia, thrombocytopenia, pancytopenia) may result, either with or without an associated hypersensitivity syndrome. (5.4)
- Suicidal behavior and ideation. (5.5)
- Medication errors involving LAMICTAL have occurred. In particular, the names LAMICTAL or lamotrigine can be confused with the names of other commonly used medications. Medication errors may also occur between the different formulations of LAMICTAL. (3.2, 5.6, 16, 17.9)

---------- ADVERSE REACTIONS ----------

- Most common adverse reactions (treatment difference ≥4%, LAMICTAL XR - Placebo) are dizziness, tremor/intention tremor, vomiting, and diplopia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 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, and primidone decrease lamotrigine concentrations by approximately 40%. (7, 12.3)
- Oral estrogen-containing contraceptives and rifampin also decrease lamotrigine concentrations by approximately 50%. (7, 12.3)

---------- USE IN SPECIFIC POPULATIONS ----------

- Pediatric use: Safety and effectiveness in patients below the age of 13 have not been established. (8.4)
- Effectiveness of lamotrigine, used as adjunctive treatment for partial seizures, was not demonstrated in a small randomized, double-blind, placebo-controlled, withdrawal study in very young pediatric patients (1 to 24 months). (8.4)
- Hepatic impairment: Dosage adjustments required. (2.1)
- Healthcare professionals can enroll patients in the Lamotrigine Pregnancy Registry (1-800-336-2176). Patients can enroll themselves in the North American Antiepileptic Drug Pregnancy Registry (1-888-233-2334). (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: April 2010

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS SKIN RASHES

LAMICTAL® XR™ can cause serious rashes requiring hospitalization and discontinuation of treatment. The incidence of these rashes, which have included Stevens-Johnson syndrome, is approximately 0.8% (8 per 1,000) in pediatric patients (2 to 16 years of age) receiving the immediate-release formulation of LAMICTAL as adjunctive therapy for epilepsy and 0.3% (3 per 1,000) in adults on adjunctive therapy for epilepsy. In a prospectively followed cohort of 1,983 pediatric patients (2 to 16 years of age) with epilepsy taking the adjunctive immediate-release formulation of LAMICTAL, there was 1 rash-related death. LAMICTAL XR is not approved for patients under the age of 13 years. 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.

The risk of serious rash caused by treatment with LAMICTAL XR is not expected to differ from that with the immediate-release formulation of LAMICTAL. However, the relatively limited treatment experience with LAMICTAL XR makes it difficult to characterize the frequency and risk of serious rashes caused by treatment with LAMICTAL XR.

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

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

Although benign rashes are also caused by LAMICTAL XR, it is not possible to predict reliably which rashes will prove to be serious or life-threatening. Accordingly, LAMICTAL XR 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

LAMICTAL XR is indicated as adjunctive therapy for primary generalized tonic-clonic (PGTC) seizures and partial onset seizures with or without secondary generalization in patients ≥13 years of age.

Safety and effectiveness of LAMICTAL XR for use in patients below the age of 13 have not been established.

2 DOSAGE AND ADMINISTRATION

LAMICTAL XR Extended-Release Tablets are taken once daily, with or without food. Tablets must be swallowed whole and must not be chewed, crushed, or divided.

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 LAMICTAL XR with valproate, (2) exceeding the recommended initial dose of LAMICTAL XR, or (3) exceeding the recommended dose escalation for LAMICTAL XR. 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 of LAMICTAL XR is exceeded and in patients with a history of allergy or rash to other AEDs.

LAMICTAL XR Patient Titration Kits provide LAMICTAL XR at doses consistent with the recommended titration schedule for the first 5 weeks of treatment, based upon concomitant medications for patients with partial onset seizures and are intended to help reduce the potential for rash. The use of LAMICTAL XR Patient Titration Kits is recommended for appropriate patients who are starting or restarting LAMICTAL XR *[see How Supplied/Storage and Handling (16)]*.

It is recommended that LAMICTAL XR 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 LAMICTAL XR, 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)]*.

LAMICTAL XR Added to Drugs Known to Induce or Inhibit Glucuronidation: Drugs other than those listed in the Clinical Pharmacology section *[see Clinical Pharmacology (12.3)]* have not been systematically evaluated in combination with lamotrigine. 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 and doses of LAMICTAL XR may require adjustment based on clinical response.

Target Plasma Levels: A therapeutic plasma concentration range has not been established for lamotrigine. Dosing of LAMICTAL XR should be based on therapeutic response *[see Clinical Pharmacology (12.3)]*.

Women Taking Estrogen-Containing Oral Contraceptives: *Starting LAMICTAL XR 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 LAMICTAL XR 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 LAMICTAL XR based on the concomitant AED or other concomitant medications (see Table 1). See below for adjustments to maintenance doses of LAMICTAL XR in women taking estrogen-containing oral contraceptives.

Adjustments to the Maintenance Dose of LAMICTAL XR In Women Taking Estrogen-Containing Oral Contraceptives:

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

(2) Starting Estrogen-Containing Oral Contraceptives: In women taking a stable dose of LAMICTAL XR and not taking carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin that induce lamotrigine glucuronidation *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*, the maintenance dose will in most cases need to be increased by as much as 2-fold in order to maintain a consistent lamotrigine plasma level. The dose increases should begin at the same time that the oral contraceptive is introduced and continue, based on clinical response, no more rapidly than 50 to 100 mg/day every week. Dose increases should not exceed the recommended rate (see Table 1) unless lamotrigine plasma levels or clinical response support larger increases. Gradual transient increases in lamotrigine plasma levels may occur during the week of inactive hormonal preparation ("pill-free" week), and these increases will be greater if dose increases are made in the days before or during the week of inactive hormonal preparation. Increased lamotrigine plasma levels could result in additional adverse reactions, such as dizziness, ataxia, and diplopia. If adverse reactions attributable to LAMICTAL XR 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 LAMICTAL XR in addition to carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin that induce lamotrigine

glucuronidation *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*, no adjustment to should be necessary to the dose of LAMICTAL XR.

(3) Stopping Estrogen-Containing Oral Contraceptives: For women not taking carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin that induce lamotrigine glucuronidation *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*, the maintenance dose of LAMICTAL XR 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 LAMICTAL XR 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 Clinical Pharmacology (12.3)]*. For women taking LAMICTAL XR in addition to carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin that induce lamotrigine glucuronidation *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*, no adjustment to the dose of LAMICTAL XR 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 ethinylestradiol, not progestogens, increased the clearance of lamotrigine up to 2-fold, and the progestin-only pills had no effect on lamotrigine plasma levels. Therefore, adjustments to the dosage of LAMICTAL XR 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 impairment *[see Use in Specific Populations (8.6), 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.

Patients With Renal Impairment: Initial doses of LAMICTAL XR should be based on patients' concomitant medications (see Table 1); reduced maintenance doses may be effective for patients with significant renal impairment *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*. Few patients with severe renal impairment have been evaluated during chronic treatment with immediate-release lamotrigine. Because there is inadequate experience in this population, LAMICTAL XR should be used with caution in these patients.

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

If a decision is made to discontinue therapy with LAMICTAL XR, a step-wise reduction of dose over at least 2 weeks (approximately 50% per week) is recommended unless safety concerns require a more rapid withdrawal *[see Warnings and Precautions (5.8)]*.

Discontinuing carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin that induce lamotrigine glucuronidation should prolong the half-life of lamotrigine; discontinuing valproate should shorten the half-life of lamotrigine.

2.2 Primary Generalized Tonic-Clonic and Partial Onset Seizures

This section provides specific dosing recommendations for patients ≥13 years of age. Specific dosing recommendations are provided depending upon concomitant AED or other concomitant medications.

Table 1. Escalation Regimen for LAMICTAL XR in Patients ≥13 Years of Age

	For Patients TAKING Valproate[a]	For Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone,[b] or Valproate[a]	For Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone[b] and NOT TAKING Valproate[a]
Weeks 1 and 2	25 mg every *other* day	25 mg every day	50 mg every day
Weeks 3 and 4	25 mg every day	50 mg every day	100 mg every day
Week 5	50 mg every day	100 mg every day	200 mg every day
Week 6	100 mg every day	150 mg every day	300 mg every day
Week 7	150 mg every day	200 mg every day	400 mg every day
Maintenance Range (Week 8 and onward)	200 to 250 mg every day[c]	300 to 400 mg every day[c]	400 to 600 mg every day[c]

[a] Valproate has been shown to inhibit glucuronidation and decrease the apparent clearance of lamotrigine *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*.

[b] These drugs induce glucuronidation and increase clearance *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*. Other drugs which have similar effects include estrogen-containing oral contraceptives *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*. Dosing recommendations for oral contraceptives can be found in General Dosing Considerations *[see Dosage and Administration (2.1)]*. Patients on rifampin, or other drugs that induce glucuronidation and increase clearance, should follow the same dosing titration/maintenance regimen as that used with anticonvulsants that have this effect.

[c] Dose increases at week 8 or later should not exceed 100 mg daily at weekly intervals.

2.3 Conversion From Immediate-Release Lamotrigine Tablets to LAMICTAL XR

Patients may be converted directly from immediate-release lamotrigine to LAMICTAL XR Extended-Release Tablets. The initial dose of LAMICTAL XR should match the total daily dose of immediate-release lamotrigine. However, some subjects on concomitant enzyme-inducing agents may have lower plasma levels of lamotrigine on conversion and should be monitored *[see Clinical Pharmacology (12.3)]*.

Following conversion to LAMICTAL XR, all patients (but especially those on drugs that induce lamotrigine glucuronidation) should be closely monitored for seizure control *[see Drug Interactions (7)]*. Depending on the therapeutic response after conversion, the total daily dose may need to be adjusted within the recommended dosing instructions (Table 1).

3 DOSAGE FORMS AND STRENGTHS

3.1 Extended-Release Tablets

25 mg, yellow with white center, round, biconvex, film-coated tablets printed with "LAMICTAL" and "XR 25."

50 mg, green with white center, round, biconvex, film-coated tablets printed with "LAMICTAL" and "XR 50."

100 mg, orange with white center, round, biconvex, film-coated tablets printed with "LAMICTAL" and "XR 100."

200 mg, blue with white center, round, biconvex, film-coated tablets printed with "LAMICTAL" and "XR 200."

300 mg, gray with white center, caplet-shaped, film-coated tablets printed with "LAMICTAL" and "XR 300."

3.2 Potential Medication Errors

Patients should be strongly advised to visually inspect their tablets to verify that they are receiving LAMICTAL XR, as opposed to other medications, and that they are receiving the correct formulation of LAMICTAL each time they fill their prescription. Depictions of the LAMICTAL XR tablets can be found in the Medication Guide *[see Patient Counseling Information (17.10]*.

4 CONTRAINDICATIONS

LAMICTAL XR is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients *[see Boxed Warning, Warnings and Precautions (5.1), (5.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Skin Rashes *[see Boxed Warning]*

The risk of serious rash caused by treatment with LAMICTAL XR is not expected to differ from that with the immediate-release formulation of LAMICTAL *[see Boxed Warning]*. However, the relatively limited treatment experience with LAMICTAL XR makes it difficult to characterize the frequency and risk of serious rashes caused by treatment with LAMICTAL XR.

Pediatric Population: The incidence of serious rash associated with hospitalization and discontinuation of the immediate-release formulation of LAMICTAL in a prospectively followed cohort of pediatric patients (2 to 16 years of age) with epilepsy receiving adjunctive therapy with immediate-release lamotrigine was approximately 0.8% (16 of 1,983). When 14 of these cases were reviewed by 3 expert dermatologists, there was considerable disagreement as to their proper classification. To illustrate, one dermatologist considered none of the cases to be Stevens-Johnson syndrome; another assigned 7 of the 14 to this diagnosis. There was 1 rash-

related death in this 1,983-patient cohort. Additionally, there have been rare cases of toxic epidermal necrolysis with and without permanent sequelae and/or death in US and foreign postmarketing experience.

There is evidence that the inclusion of valproate in a multidrug regimen increases the risk of serious, potentially life-threatening rash in pediatric patients. In pediatric patients who used valproate concomitantly, 1.2% (6 of 482) experienced a serious rash compared with 0.6% (6 of 952) patients not taking valproate.

LAMICTAL XR is not approved in patients under the age of 13 years.

Adult Population: Serious rash associated with hospitalization and discontinuation of the immediate-release formulation of LAMICTAL occurred in 0.3% (11 of 3,348) of adult patients who received the immediate-release formulation of LAMICTAL in premarketing clinical trials of epilepsy. In worldwide postmarketing experience, rare cases of rash-related death have been reported, but their numbers are too few to permit a precise estimate of the rate.

Among the rashes leading to hospitalization were Stevens-Johnson syndrome, toxic epidermal necrolysis, angioedema, and a rash associated with a variable number of the following systemic manifestations: fever, lymphadenopathy, facial swelling, and hematologic and hepatologic abnormalities.

There is evidence that the inclusion of valproate in a multidrug regimen increases the risk of serious, potentially life-threatening rash in adults. Specifically, of 584 patients administered the immediate-release formulation of LAMICTAL with valproate in epilepsy clinical trials, 6 (1%) were hospitalized in association with rash; in contrast, 4 (0.16%) of 2,398 clinical trial patients and volunteers administered the immediate-release formulation of LAMICTAL in the absence of valproate were hospitalized.

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

5.2 Hypersensitivity Reactions

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

Prior to initiation of treatment with LAMICTAL XR, the patient should be instructed that a rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy) may herald a serious medical event and that the patient should report any such occurrence to a physician immediately.

5.3 Acute Multiorgan Failure

Multiorgan failure, which in some cases has been fatal or irreversible, has been observed in patients receiving the immediate-release formulation of LAMICTAL. Fatalities associated with multiorgan failure and various degrees of hepatic failure have been reported in 2 of 3,796 adult patients and 4 of 2,435 pediatric patients who received the immediate-release formulation of LAMICTAL in epilepsy clinical trials. Rare fatalities from multiorgan failure have been reported in compassionate plea and postmarketing use. The majority of these deaths occurred in association with other serious medical events, including status epilepticus and overwhelming sepsis, and hantavirus, making it difficult to identify the initial cause.

Additionally, 3 patients (a 45-year-old woman, a 3.5-year-old boy, and an 11-year-old girl) developed multiorgan dysfunction and disseminated intravascular coagulation 9 to 14 days after the immediate-release formulation of LAMICTAL was added to their AED regimens. Rash and elevated transaminases were also present in all patients and rhabdomyolysis was noted in 2 patients. Both pediatric patients were receiving concomitant therapy with valproate, while the adult patient was being treated with carbamazepine and clonazepam. All patients subsequently recovered with supportive care after treatment with the immediate-release formulation of LAMICTAL was discontinued.

5.4 Blood Dyscrasias

There have been reports of blood dyscrasias with the immediate-release formulation of LAMICTAL that may or may not be associated with the hypersensitivity syndrome. These have included neutropenia, leukopenia, anemia, thrombocytopenia, pancytopenia, and, rarely, aplastic anemia and pure red cell aplasia.

5.5 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including LAMICTAL XR, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately 1 case of suicidal thinking or behavior for every 530 patients treated. There were 4 suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number of events is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as 1 week after starting treatment with AEDs and persisted for the duration of treatment assessed.

Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanism of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5 to 100 years) in the clinical trials analyzed.

Table 2 shows absolute and relative risk by indication for all evaluated AEDs.

Table 2. Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

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

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing LAMICTAL XR or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

5.6 Potential Medication Errors

Medication errors involving LAMICTAL have occurred. In particular, the names LAMICTAL or lamotrigine can be confused with the names of other commonly used medications. Medication errors may also occur between the different formulations of LAMICTAL. To reduce the potential of medication errors, write and say LAMICTAL XR clearly. Depictions of the LAMICTAL XR Extended-Release Tablets can be found in the Medication Guide *[see Patient Counseling Information (17.10)]*. Each LAMICTAL XR tablet

has a distinct color and white center, and is printed with "LAMICTAL XR" and the tablet strength. These distinctive features serve to identify the different presentations of the drug and thus may help reduce the risk of medication errors. LAMICTAL XR is supplied in round, unit-of-use bottles with orange caps containing 30 tablets. The label on the bottle includes a depiction of the tablets which further communicates to patients and pharmacists that the medication is LAMICTAL XR and the specific tablet strength included in the bottle. The unit-of-use bottle with a distinctive orange cap and distinctive bottle label features serves to identify the different presentations of the drug and thus may help to reduce the risk of medication errors. To avoid the medication error of using the wrong drug or formulation, patients should be strongly advised to visually inspect their tablets to verify that they are LAMICTAL XR each time they fill their prescription.

5.7 Concomitant Use With Oral Contraceptives

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

5.8 Withdrawal Seizures

As with other AEDs, LAMICTAL XR should not be abruptly discontinued. In patients with epilepsy there is a possibility of increasing seizure frequency. Unless safety concerns require a more rapid withdrawal, the dose of LAMICTAL XR should be tapered over a period of at least 2 weeks (approximately 50% reduction per week) *[see Dosage and Administration (2.1)]*.

5.9 Status Epilepticus

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

5.10 Sudden Unexplained Death in Epilepsy (SUDEP)

During the premarketing development of the immediate-release formulation of LAMICTAL, 20 sudden and unexplained deaths were recorded among a cohort of 4,700 patients with epilepsy (5,747 patient-years of exposure).

Some of these could represent seizure-related deaths in which the seizure was not observed, e.g., at night. This represents an incidence of 0.0035 deaths per patient-year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not

receiving lamotrigine (ranging from 0.0005 for the general population of patients with epilepsy, to 0.004 for a recently studied clinical trial population similar to that in the clinical development program for immediate-release lamotrigine, to 0.005 for patients with refractory epilepsy). Consequently, whether these figures are reassuring or suggest concern depends on the comparability of the populations reported upon to the cohort receiving immediate-release lamotrigine and the accuracy of the estimates provided. Probably most reassuring is the similarity of estimated SUDEP rates in patients receiving immediate-release lamotrigine and those receiving other AEDs, chemically unrelated to each other, that underwent clinical testing in similar populations. Importantly, that drug is chemically unrelated to lamotrigine. This evidence suggests, although it certainly does not prove, that the high SUDEP rates reflect population rates, not a drug effect.

5.11 Addition of LAMICTAL XR to a Multidrug Regimen That Includes Valproate

Because valproate reduces the clearance of lamotrigine, the dosage of lamotrigine in the presence of valproate is less than half of that required in its absence.

5.12 Binding in the Eye and Other Melanin-Containing Tissues

Because lamotrigine binds to melanin, it could accumulate in melanin-rich tissues over time. This raises the possibility that lamotrigine may cause toxicity in these tissues after extended use. Although ophthalmological testing was performed in one controlled clinical trial, the testing was inadequate to exclude subtle effects or injury occurring after long-term exposure. Moreover, the capacity of available tests to detect potentially adverse consequences, if any, of lamotrigine binding to melanin is unknown *[see Clinical Pharmacology (12.2)]*.

Accordingly, although there are no specific recommendations for periodic ophthalmological monitoring, prescribers should be aware of the possibility of long-term ophthalmologic effects.

5.13 Laboratory Tests

The value of monitoring plasma concentrations of lamotrigine in patients treated with LAMICTAL XR has not been established. Because of the possible pharmacokinetic interactions between lamotrigine and other drugs including AEDs (see Table 4), monitoring of the plasma levels of lamotrigine and concomitant drugs may be indicated, particularly during dosage adjustments. In general, clinical judgment should be exercised regarding monitoring of plasma levels of lamotrigine and other drugs and whether or not dosage adjustments are necessary.

Treatment with LAMICTAL XR caused an increased incidence of subnormal (below the reference range) values in some hematology analytes (e.g., total white blood cells, monocytes). The treatment effect (LAMICTAL XR % - Placebo %) incidence of subnormal counts was 3% for total white blood cells and 4% for monocytes.

6 ADVERSE REACTIONS

The following adverse reactions are described in more detail in the *Warnings and Precautions* section of the label:

- Serious skin rashes *[see Warnings and Precautions (5.1)]*

- Hypersensitivity reactions *[see Warnings and Precautions (5.2)]*
- Acute multiorgan failure *[see Warnings and Precautions (5.3)]*
- Blood dyscrasias *[see Warnings and Precautions (5.4)]*
- Suicidal behavior and ideation *[see Warnings and Precautions (5.5)]*
- Withdrawal seizures *[see Warnings and Precautions (5.8)]*
- Status epilepticus *[see Warnings and Precautions (5.9)]*
- Sudden unexplained death in epilepsy *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trial Experience With LAMICTAL XR for Treatment of PGTC and Partial Onset Seizures

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

LAMICTAL XR has been evaluated for safety in patients ≥13 years of age with PGTC and partial onset seizures. The most commonly observed adverse reactions (≥4% for LAMICTAL XR and more common on drug than placebo) in these 2 double-blind, placebo-controlled trials of adjunctive therapy with LAMICTAL XR were, in order of decreasing treatment difference (LAMICTAL XR % - Placebo %) incidence: dizziness, tremor/intention tremor, vomiting, and diplopia.

In these 2 trials, adverse reactions led to withdrawal of 4 (2%) patients in the group receiving placebo and 10 (5%) patients in the group receiving LAMICTAL XR. Dizziness was the most common reason for withdrawal in the group receiving LAMICTAL XR (5 patients [3%]). The next most common adverse reactions leading to withdrawal in 2 patients each (1%) were rash, headache, nausea, and nystagmus.

Table 3 displays the incidence of adverse reactions in these two 19-week, double-blind, placebo-controlled studies of patients with PGTC and partial onset seizures.

Table 3. Treatment-Emergent Adverse Reaction Incidence in Double-Blind, Placebo-Controlled Adjunctive Trials of Patients With Epilepsy (Adverse Reactions ≥2% of Patients Treated With LAMICTAL XR and Numerically More Frequent Than in the Placebo Group)

Body System/Adverse Reaction	LAMICTAL XR (n = 190) %	Placebo (n = 195) %
Ear and Labyrinth Disorders		
Vertigo	3	<1
Eye Disorders		
Diplopia	5	<1
Vision blurred	3	2
Gastrointestinal Disorders		
Nausea	7	4

Vomiting	6	3
Diarrhea	5	3
Constipation	2	<1
Dry mouth	2	1
General Disorders and Administration Site Conditions		
Asthenia and fatigue	6	4
Infections and Infestations		
Sinusitis	2	1
Metabolic and Nutritional Disorders		
Anorexia	3	2
Musculoskeletal and Connective Tissue Disorder		
Myalgia	2	0
Nervous System		
Dizziness	14	6
Tremor and intention tremor	6	1
Somnolence	5	3
Cerebellar coordination and balance disorder	3	0
Nystagmus	2	<1
Psychiatric Disorders		
Depression	3	<1
Anxiety	3	0
Respiratory, Thoracic, and Mediastinal Disorders		
Pharyngolaryngeal pain	3	2
Vascular disorder		
Hot flush	2	0

Note: In these trials the incidence of nonserious rash was 2% for LAMICTAL XR and 3% for placebo. In clinical trials evaluating the immediate-release formulation of LAMICTAL, the rate of serious rash was 0.3% in adults on adjunctive therapy for epilepsy *[see Boxed Warning]*.

Adverse reactions were also analyzed to assess the incidence of the onset of an event in the titration period, and in the maintenance period, and if adverse reactions occurring in the titration phase persisted in the maintenance phase.

The incidence for many adverse reactions caused by LAMICTAL XR treatment was increased relative to placebo (i.e., LAMICTAL XR % - Placebo % = treatment difference ≥2%) in either the titration or maintenance phases of the study. During the titration phase, an increased incidence (shown in descending order of % treatment difference) was observed for diarrhea,

nausea, vomiting, somnolence, vertigo, myalgia, hot flush, and anxiety. During the maintenance phase, an increased incidence was observed for dizziness, tremor, and diplopia. Some adverse reactions developing in the titration phase were notable for persisting (>7 days) into the maintenance phase. These "persistent" adverse reactions included somnolence and dizziness.

There were inadequate data to evaluate the effect of dose and/or concentration on the incidence of adverse reactions because although patients were randomized to different target doses based upon concomitant AED, the plasma exposure was expected to be generally similar among all patients receiving different doses. However, in a randomized, parallel study comparing placebo and 300 and 500 mg/day of immediate-release formulation of LAMICTAL, the incidence of the most common adverse reactions (≥5%) such as ataxia, blurred vision, diplopia, and dizziness were dose-related. Less common adverse reactions (<5%) were not assessed for dose-response relationships.

There were insufficient data to evaluate the effect of gender, age, and race on the adverse reaction profile for LAMICTAL XR.

6.2 Other Adverse Reactions Observed During the Clinical Development of the Immediate-Release Formulation of LAMICTAL

All reported reactions are included except those already listed in the previous tables or elsewhere in the labeling, those too general to be informative, and those not reasonably associated with the use of the drug.

Adjunctive Therapy in Adults With Epilepsy: In addition to the adverse reactions reported above from the development of LAMICTAL XR, the following adverse reactions with an uncertain relationship to lamotrigine were reported during the clinical development of the immediate-release formulation of LAMICTAL for treatment of epilepsy in adults. These reactions occurred in ≥2% of patients receiving the immediate-release formulation of LAMICTAL and more frequently than in the placebo group.

Body as a Whole: Flu syndrome, fever, abdominal pain, neck pain.

Musculoskeletal: Arthralgia.

Nervous: Insomnia, convulsion, irritability, speech disorder, concentration disturbance.

Respiratory: Rhinitis, pharyngitis, cough increased.

Skin and Appendages: Rash, pruritus.

Urogenital: (female patients only) Vaginitis, amenorrhea, dysmenorrhea.

Other Clinical Trial Experience: The immediate-release formulation of LAMICTAL has been administered to 6,694 individuals for whom complete adverse reaction data was captured during all clinical trials, only some of which were placebo controlled. During these trials, all adverse reactions were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse reactions, similar types of reactions were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. The frequencies presented

represent the proportion of the 6,694 individuals exposed to LAMICTAL who experienced an event of the type cited on at least one occasion while receiving LAMICTAL.

Adverse reactions are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* adverse reactions are defined as those occurring in at least 1/100 patients; *infrequent* adverse reactions are those occurring in 1/100 to 1/1,000 patients; *rare* adverse reactions are those occurring in fewer than 1/1,000 patients.

Body as a Whole: *Infrequent:* Allergic reaction, chills, and malaise.

Cardiovascular System: *Infrequent:* Flushing, hypertension, palpitations, postural hypotension, syncope, tachycardia, and vasodilation.

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

Digestive System: *Infrequent:* Dysphagia, eructation, gastritis, gingivitis, increased appetite, increased salivation, liver function tests abnormal, and mouth ulceration. *Rare:* Gastrointestinal hemorrhage, glossitis, gum hemorrhage, gum hyperplasia, hematemesis, hemorrhagic colitis, hepatitis, melena, stomach ulcer, stomatitis, and tongue edema.

Endocrine System: *Rare:* Goiter and hypothyroidism.

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

Metabolic and Nutritional Disorders: *Infrequent:* Aspartate transaminase increased. *Rare:* Alcohol intolerance, alkaline phosphatase increase, alanine transaminase increase, bilirubinemia, general edema, gamma glutamyl transpeptidase increase, and hyperglycemia.

Musculoskeletal System: *Infrequent:* Arthritis, leg cramps, myasthenia, and twitching. *Rare:* Bursitis, muscle atrophy, pathological fracture, and tendinous contracture.

Nervous System: *Frequent:* Confusion and paresthesia. *Infrequent:* Akathisia, apathy, aphasia, CNS depression, depersonalization, dysarthria, dyskinesia, euphoria, hallucinations, hostility, hyperkinesia, hypertonia, libido decreased, memory decrease, mind racing, movement disorder, myoclonus, panic attack, paranoid reaction, personality disorder, psychosis, stupor, and suicidal ideation. *Rare:* Choreoathetosis, delirium, delusions, dysphoria, dystonia, extrapyramidal syndrome, faintness, grand mal convulsions, hemiplegia, hyperalgesia, hyperesthesia, hypokinesia, hypotonia, manic depression reaction, muscle spasm, neuralgia, neurosis, paralysis, and peripheral neuritis.

Respiratory System: *Infrequent:* Yawn. *Rare:* Hiccup and hyperventilation.

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

Urogenital System: *Infrequent:* Abnormal ejaculation, hematuria, impotence, menorrhagia, polyuria, urinary incontinence. *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 with the Immediate-Release Formulation of LAMICTAL

The following adverse events (not listed above in clinical trials or other sections of the prescribing information) have been identified during postapproval use of the immediate-release formulation of LAMICTAL. Because these events 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.

Gastrointestinal: Esophagitis.

Hepatobiliary Tract and Pancreas: Pancreatitis.

Immunologic: Lupus-like reaction, vasculitis.

Lower Respiratory: Apnea.

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

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

Non-site Specific: Progressive immunosuppression.

7 DRUG INTERACTIONS

Significant drug interactions with lamotrigine are summarized in Table 4. Additional details of these drug interaction studies, which were conducted using the immediate-release formulation of LAMICTAL, are provided in the Clinical Pharmacology section *[see Clinical Pharmacology (12.3)]*.

Table 4. 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	Decreased lamotrigine levels approximately 50%.
	↓ levonorgestrel	Decrease in levonorgestrel component by

		19%.
Carbamazepine (CBZ) and CBZ epoxide	↓ lamotrigine ? CBZ epoxide	Addition of carbamazepine decreases lamotrigine concentration approximately 40%. May increase CBZ epoxide levels.
Phenobarbital/Primidone	↓ lamotrigine	Decreased lamotrigine concentration approximately 40%.
Phenytoin (PHT)	↓ lamotrigine	Decreased lamotrigine concentration approximately 40%.
Rifampin	↓ lamotrigine	Decreased lamotrigine AUC approximately 40%.
Valproate	↑ lamotrigine ? valproate	Increased lamotrigine concentrations slightly more than 2-fold. Decreased valproate concentrations an average of 25% over a 3-week period then stabilized in healthy volunteers; no change in controlled clinical trials in epilepsy patients.

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

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

When pregnant rats were orally dosed at 0.1, 0.14, or 0.3 times the highest human maintenance dose (on a mg/m^2 basis) during the latter part of gestation (days 15 to 20), maternal toxicity and fetal death were seen. In dams, food consumption and weight gain were reduced, and the gestation period was slightly prolonged (22.6 vs. 22.0 days in the control group). Stillborn pups were found in all 3 drug-treated groups with the highest number in the high-dose group. Postnatal death was also seen, but only in the 2 highest doses, and occurred between days 1 and 20. Some of these deaths appear to be drug-related and not secondary to the maternal toxicity. A no-observed-effect level (NOEL) could not be determined for this study.

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

Non-Teratogenic Effects: 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-partum concentrations after delivery. Dosage adjustments may be necessary to maintain clinical response.

Pregnancy Exposure Registry: To provide information regarding the effects of in utero exposure to LAMICTAL XR, physicians are advised to recommend that pregnant patients taking LAMICTAL XR enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll-free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

Physicians are also encouraged to register patients in the Lamotrigine Pregnancy Registry; enrollment in this registry must be done prior to any prenatal diagnostic tests and **before fetal outcome is known**. **Physicians** can obtain information by calling the Lamotrigine Pregnancy Registry at 1-800-336-2176 (toll-free).

8.2 Labor and Delivery

The effect of LAMICTAL XR on labor and delivery in humans is unknown.

8.3 Nursing Mothers

Preliminary data indicate that lamotrigine passes into human milk. Because the effects on the infant exposed to lamotrigine by this route are unknown, breastfeeding while taking LAMICTAL XR is not recommended.

8.4 Pediatric Use

LAMICTAL XR is indicated as adjunctive therapy for PGTC and partial onset seizures with or without secondary generalization in patients ≥13 years of age. Safety and effectiveness of LAMICTAL XR for any use in patients below the age of 13 have not been established.

The immediate-release formulation of LAMICTAL is indicated for adjunctive therapy in patients ≥2 years of age for partial seizures, the generalized seizures of Lennox-Gastaut syndrome, and primary generalized tonic-clonic seizures.

Safety and efficacy of the immediate-release formulation of LAMICTAL, used as adjunctive treatment for partial seizures, were not demonstrated in a small randomized, double-blind, placebo-controlled, withdrawal study in very young pediatric patients (1 to 24 months). The immediate-release formulation of LAMICTAL was associated with an increased risk for infectious adverse reactions (LAMICTAL 37%, Placebo 5%), and respiratory adverse reactions (LAMICTAL 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.

8.5 Geriatric Use

Clinical studies of LAMICTAL XR for epilepsy did not include sufficient numbers of subjects 65 years of age and over to determine whether they respond differently from younger subjects 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 Patients With Hepatic Impairment

Experience in patients with hepatic impairment is limited. Based on a clinical pharmacology study with the immediate-release formulation of LAMICTAL in 24 patients 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 Patients With 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 immediate-release lamotrigine in patients with varying degrees of renal impairment with healthy volunteers, the plasma half-life of lamotrigine was significantly longer in the patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

Initial doses of LAMICTAL XR 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, LAMICTAL XR should be used with caution in these patients *[see Dosage and Administration (2.1)]*.

10 OVERDOSAGE

10.1 Human Overdose Experience

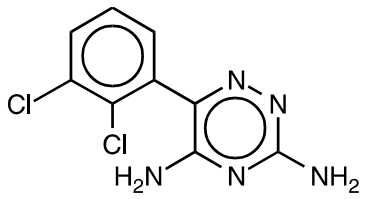
Overdoses involving quantities up to 15 g have been reported for the immediate-release formulation of LAMICTAL, some of which have been fatal. Overdose has resulted in ataxia, nystagmus, increased seizures, decreased level of consciousness, coma, and intraventricular conduction delay.

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 or gastric lavage should be performed; usual precautions should be taken to protect the airway. 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 LAMICTAL XR.

11 DESCRIPTION

LAMICTAL XR (lamotrigine), an AED of the phenyltriazine class, is chemically unrelated to existing AEDs. Its 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 is a white to pale cream-colored powder and has a pK_a of 5.7. Lamotrigine 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:



LAMICTAL XR Extended-Release Tablets are supplied for oral administration as 25-mg (yellow with white center), 50-mg (green with white center), 100-mg (orange with white center), 200-mg (blue with white center), and 300-mg (gray with white center) tablets. Each tablet contains the labeled amount of lamotrigine and the following inactive ingredients: glycerol monostearate, hypromellose, lactose monohydrate; magnesium stearate; methacrylic acid copolymer dispersion, polyethylene glycol 400, polysorbate 80, silicon dioxide (25-mg and 50-mg tablets only), titanium dioxide, triethyl citrate, iron oxide black (50-mg and 300-mg tablets only), iron oxide yellow (25-mg, 50-mg, 100-mg tablets only), iron oxide red (100-mg tablet

only), FD&C Blue No. 2 Aluminum Lake (200-mg tablet only). Tablets are printed with edible black ink.

LAMICTAL XR Extended-Release Tablets contain a modified-release eroding formulation as the core. The tablets are coated with a clear enteric coat and have an aperture drilled through the coats on both faces of the tablet (DiffCORE™) to enable a controlled release of drug in the acidic environment of the stomach. The combination of this and the modified-release core are designed to control the dissolution rate of lamotrigine over a period of approximately 12 to 15 hours, leading to a gradual increase in serum lamotrigine levels.

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).

Although the relevance for human use is unknown, the following data characterize the performance of lamotrigine in receptor binding assays. Lamotrigine had a weak inhibitory effect on the serotonin 5-HT_3 receptor (IC_{50} = 18 µM). It does not exhibit high affinity binding (IC_{50}>100 µM) to the following neurotransmitter receptors: adenosine A_1 and A_2; adrenergic α_1, α_2, and β; dopamine D_1 and D_2; γ-aminobutyric acid (GABA) A and B; histamine H_1; kappa opioid; muscarinic acetylcholine; and serotonin 5-HT_2. Studies have failed to detect an effect of lamotrigine on dihydropyridine-sensitive calcium channels. It had weak effects at sigma opioid receptors (IC_{50} = 145 µM). Lamotrigine did not inhibit the uptake of norepinephrine, dopamine, or serotonin, (IC_{50}>200 µM) when tested in rat synaptosomes and/or human platelets in vitro.

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.

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.

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.

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

12.3 Pharmacokinetics

In comparison to immediate-release lamotrigine, the plasma lamotrigine levels following administration of LAMICTAL XR are not associated with any significant changes in trough plasma concentrations, and are characterized by lower peaks, longer time to peaks, and lower peak-to-trough fluctuation, as described in detail below.

Absorption: Lamotrigine is absorbed after oral administration with negligible first-pass metabolism. The bioavailability of lamotrigine is not affected by food.

In an open-label, crossover study of 44 subjects with epilepsy receiving concomitant AEDs, the steady-state pharmacokinetics of lamotrigine were compared following administration of equivalent total doses of LAMICTAL XR given once daily with those of lamotrigine immediate-release given twice daily. In this study, the median time to peak concentration (T_{max}) following administration of LAMICTAL XR was 4 to 6 hours in patients taking carbamazepine, phenytoin, phenobarbital, or primidone; 9 to 11 hours in patients taking VPA; and 6 to 10 hours in patients taking AEDs other than carbamazepine, phenytoin, phenobarbital, primidone, or VPA. In comparison, the median T_{max} following administration of immediate-release lamotrigine was between 1 and 1.5 hours.

The steady-state trough concentrations for extended-release lamotrigine were similar to or higher than those of immediate-release lamotrigine depending on concomitant AED (Table 5).

A mean reduction in the lamotrigine C_{max} by 11% to 29% was observed for LAMICTAL XR compared to immediate-release lamotrigine resulting in a decrease in the peak-to-trough fluctuation in serum lamotrigine concentrations. However, in some subjects receiving enzyme-inducing AEDs, a reduction in C_{max} of 44% to 77% was observed. The degree of fluctuation was reduced by 17% in patients taking enzyme-inducing AEDs, 34% in patients taking VPA, and 37% in patients taking AEDs other than carbamazepine, phenytoin, phenobarbital, primidone, or VPA. LAMICTAL XR and immediate-release lamotrigine regimens were similar with respect to area under the curve (AUC, a measure of the extent of bioavailability) for patients receiving AEDs other than those known to induce the metabolism of lamotrigine. The relative bioavailability of extended-release lamotrigine was approximately 21% lower than immediate-release lamotrigine in subjects receiving enzyme-inducing AEDs. However, in some subjects in this group a reduction in exposure of up to 70% was observed when switched to LAMICTAL XR. Therefore, doses may need to be adjusted in some subjects based on therapeutic response.

Table 5. Steady-State Bioavailability of LAMICTAL XR Relative to Immediate-Release Lamotrigine at Equivalent Daily Doses (Ratio of XR to IR 90% CI)

Concomitant AED	AUC $_{(0\text{-}24ss)}$	C_{max}	C_{min}
EIAEDs[a]	0.79 (0.69, 0.90)	0.71 (0.61, 0.82)	0.99 (0.89, 1.09)
VPA	0.94 (0.81, 1.08)	0.88 (0.75, 1.03)	0.99 (0.88, 1.10)
AEDs other than EIAEDs[a] or VPA	1.00 (0.88, 1.14)	0.89 (0.78, 1.03)	1.14 (1.03, 1.25)

[a] EIAEDs include carbamazepine, phenytoin, phenobarbital, and primidone.

Dose Proportionality: In healthy volunteers not receiving any other medications and given LAMICTAL XR once daily, the systemic exposure to lamotrigine increased in direct proportion to the dose administered over the range of 50 to 200 mg. At doses between 25 and 50 mg, the increase was less than dose proportional, with a 2-fold increase in dose resulting in an approximately 1.6-fold increase in systemic exposure.

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 that induce lamotrigine glucuronidation *[see Drug Interactions (7)]*.

Elimination: The elimination half-life and apparent clearance of lamotrigine following administration of immediate-release lamotrigine to adult patients with epilepsy and healthy volunteers is summarized in Table 6. Half-life and apparent oral clearance vary depending on concomitant AEDs.

Since the half-life of lamotrigine following administration of single doses of immediate-release lamotrigine is comparable to that observed following administration of LAMICTAL XR, similar changes in the half-life of lamotrigine would be expected for LAMICTAL XR.

Table 6. Mean[a] Pharmacokinetic Parameters of Immediate-Release Lamotrigine in Healthy Volunteers and Adult Patients With Epilepsy

Adult Study Population	Number of Subjects	$t_{½}$: Elimination Half-life (hr)	Cl/F: Apparent Plasma Clearance (mL/min/kg)
Healthy volunteers taking no other medications:			
Single-dose lamotrigine	179	32.8 (14.0-103.0)	0.44 (0.12-1.10)
Multiple-dose lamotrigine	36	25.4 (11.6-61.6)	0.58 (0.24-1.15)

Healthy volunteers taking valproate:			
Single-dose lamotrigine	6	48.3 (31.5-88.6)	0.30 (0.14-0.42)
Multiple-dose lamotrigine	18	70.3 (41.9-113.5)	0.18 (0.12-0.33)
Patients with epilepsy taking valproate only:			
Single-dose lamotrigine	4	58.8 (30.5-88.8)	0.28 (0.16-0.40)
Patients with epilepsy taking carbamazepine, phenytoin, phenobarbital, or primidone[b] plus valproate:			
Single-dose lamotrigine	25	27.2 (11.2-51.6)	0.53 (0.27-1.04)
Patients with epilepsy taking carbamazepine, phenytoin, phenobarbital, or primidone: [b]			
Single-dose lamotrigine	24	14.4 (6.4-30.4)	1.10 (0.51-2.22)
Multiple-dose lamotrigine	17	12.6 (7.5-23.1)	1.21 (0.66-1.82)

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

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

Drug Interactions: The apparent clearance of lamotrigine is affected by the coadministration of certain medications *[see Warnings and Precautions (5.7, 5.11), Drug Interactions (7)]*.

The net effects of drug interactions with lamotrigine are summarized in Table 7. Details of the drug interaction studies, which were done using immediate-release lamotrigine, are provided following Table 7.

Table 7. 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]	↓
Bupropion	Not assessed	↔
Carbamazepine (CBZ)	↔	↓
CBZ epoxide[e]	?	
Felbamate	Not assessed	↔
Gabapentin	Not assessed	↔
Levetiracetam	↔	↔
Lithium	↔	Not assessed
Olanzapine	↔	↔[f]
Oxcarbazepine	↔	↔
10-monohydroxy oxcarbazepine metabolite[g]	↔	
Phenobarbital/primidone	↔	↓
Phenytoin (PHT)	↔	↓
Pregabalin	↔	↔
Rifampin	Not assessed	↓
Topiramate	↔[h]	↔
Valproate	↓	↑
Valproate + PHT and/or CBZ	Not assessed	↔
Zonisamide	Not assessed	↔

[a] From adjunctive clinical trials and volunteer studies.

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

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

[d] Modest decrease in levonorgestrel.

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

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

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

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

↔ = No significant effect.

? = Conflicting data.

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

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

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 LAMICTAL XR in the presence of progestogens alone will likely not be needed.

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%.

Esomeprazole: In a study of 30 subjects, coadministration of LAMICTAL XR with esomeprazole resulted in no significant change in lamotrigine levels and a small decrease in T_{max}. The levels of gastric pH were not altered compared with pre-lamotrigine dosing.

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

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

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

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

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

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

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

Oxcarbazepine: The AUC and C_{max} of oxcarbazepine and its active 10-monohydroxy oxcarbazepine metabolite were not significantly different following the addition of oxcarbazepine (600 mg twice daily) to lamotrigine (200 mg once daily) in healthy male

volunteers (n = 13) compared with healthy male volunteers receiving oxcarbazepine alone (n = 13).

In the same study, the AUC and C_{max} of lamotrigine were similar following the addition of oxcarbazepine (600 mg twice daily) to 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.

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

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

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

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

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

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

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

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

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

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

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

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

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

Elderly: The pharmacokinetics of lamotrigine following a single 150 mg dose of immediate-release 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).

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

Race: The apparent oral clearance of lamotrigine was 25% lower in non-Caucasians than Caucasians.

Pediatric Patients: Safety and effectiveness of LAMICTAL XR for use in patients below the age of 13 have not been established.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenicity was seen in 1 mouse study or 2 rat studies following oral administration of lamotrigine for up to 2 years at maximum tolerated doses (30 mg/kg/day for mice and 10 to 15 mg/kg/day for rats, doses that are equivalent to 90 mg/m^2 and 60 to 90 mg/m^2,

respectively). Steady-state plasma concentrations ranged from 1 to 4 mcg/mL in the mouse study and 1 to 10 mcg/mL in the rat study. Plasma concentrations associated with the recommended human doses of 300 to 500 mg/day are generally in the range of 2 to 5 mcg/mL, but concentrations as high as 19 mcg/mL have been recorded.

Lamotrigine was not mutagenic in the presence or absence of metabolic activation when tested in 2 gene mutation assays (the Ames test and the in vitro mammalian mouse lymphoma assay). In 2 cytogenetic assays (the in vitro human lymphocyte assay and the in vivo rat bone marrow assay), lamotrigine did not increase the incidence of structural or numerical chromosomal abnormalities.

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

14 CLINICAL STUDIES

14.1 PGTC Seizures

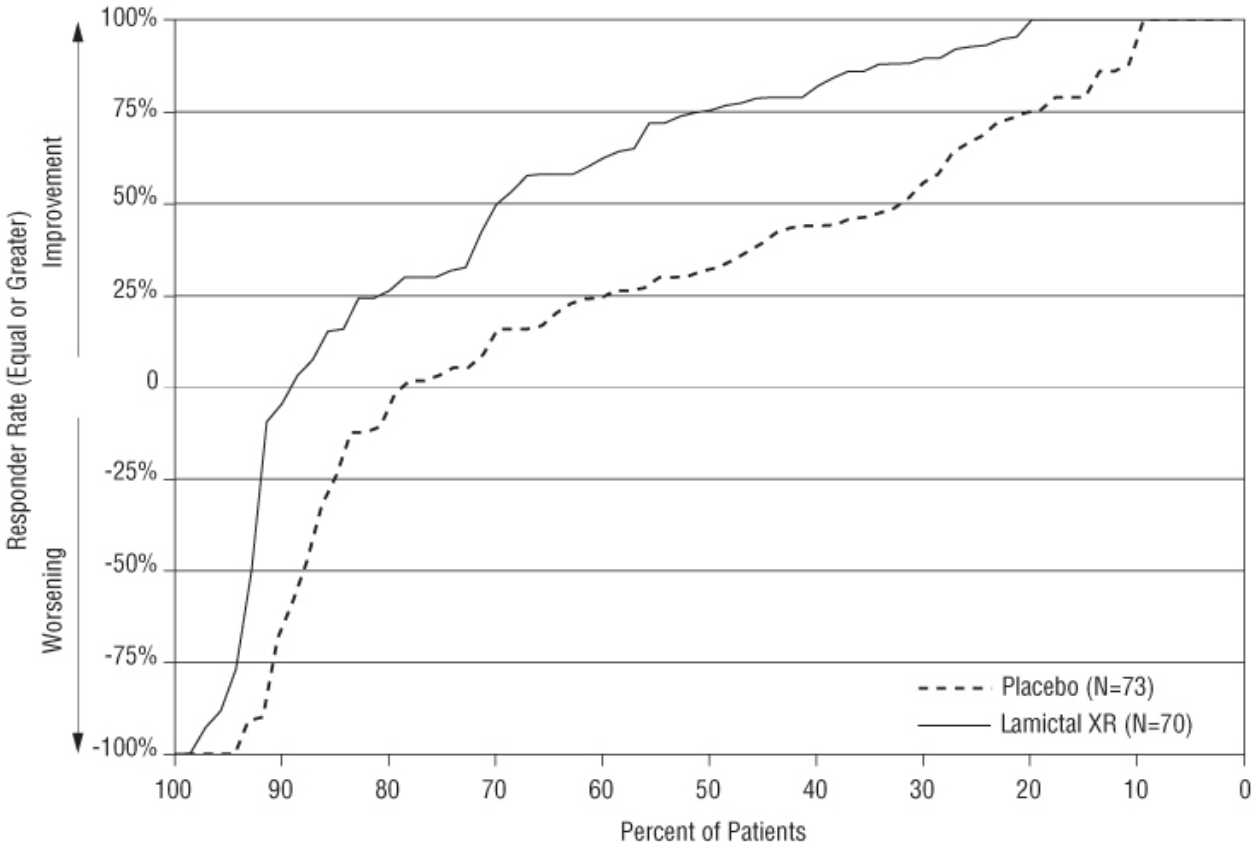
The effectiveness of LAMICTAL XR as adjunctive therapy was established in PGTC seizures in a 19-week, international, multicenter, double-blind, randomized, placebo-controlled study in 143 patients 13 years of age and older (n = 70 on LAMICTAL XR and n = 73 on placebo). Patients with at least 3 PGTC seizures during an 8-week baseline phase were randomized to 19 weeks of treatment with LAMICTAL XR 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 200 mg/day to 500 mg/day of LAMICTAL XR based on concomitant AED(s) (target dose = 200 mg for valproate, 300 mg for AEDs not altering plasma lamotrigine levels, and 500 mg for enzyme-inducing AEDs).

The primary efficacy endpoint was percent change from baseline in PGTC seizure frequency during the double-blind treatment phase. For the intent-to-treat population, the median percent reduction in PGTC seizure frequency was 75% in patients treated with LAMICTAL XR and 32% in patients treated with placebo, a difference that was statistically significant, defined as a 2-sided p value ≤ 0.05.

Figure 1 presents the percentage of patients (X-axis) with a percent reduction in PGTC seizure frequency (responder rate) from baseline through the entire treatment period at least as great as that represented on the Y-axis. A positive value on the Y-axis indicates an improvement from baseline (i.e., a decrease in seizure frequency), while a negative value indicates a worsening from baseline (i.e., an increase in seizure frequency). Thus, in a display of this type, a curve for an effective treatment is shifted to the left of the curve for placebo. The proportion of patients achieving any particular level of reduction in PGTC seizure frequency was consistently higher for the group treated with LAMICTAL XR compared with the placebo group. For example, 70% of patients randomized to LAMICTAL XR experienced a 50% or greater reduction in PGTC seizure frequency, compared with 32% of patients randomized to placebo. Patients with an

increase in seizure frequency >100% are represented on the Y-axis as equal to or greater than -100%.

Figure 1. Proportion of Patients by Responder Rate for LAMICTAL XR and Placebo Group (PGTC Study)



14.2 Partial Onset Seizures

The effectiveness of immediate-release lamotrigine as adjunctive therapy was initially established in 3 pivotal multicenter, placebo-controlled, double-blind clinical trials in 355 adults with refractory partial onset seizures.

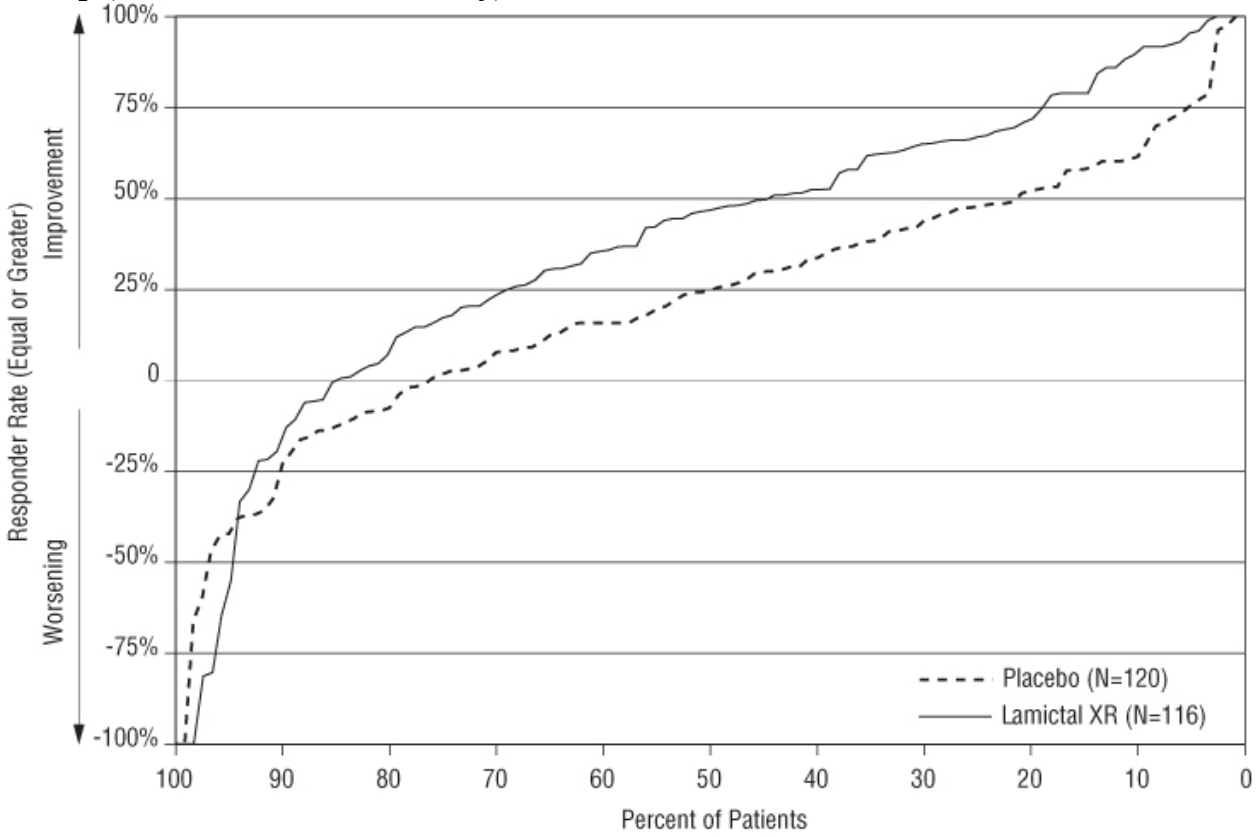
The effectiveness of LAMICTAL XR as adjunctive therapy in partial onset seizures, with or without secondary generalization, was established in a 19-week, multicenter, double-blind, placebo-controlled trial in 236 patients, 13 years of age and older (approximately 93% of patients were 16 to 65 years old). Approximately 36% were from the U.S. and approximately 64% were from other countries including Argentina, Brazil, Chile, Germany, India, Korea, Russian Federation, and Ukraine. Patients with at least 8 partial onset seizures during an 8-week prospective baseline phase (or 4-week prospective baseline coupled with a 4-week historical baseline documented with seizure diary data) were randomized to treatment with LAMICTAL XR (n = 116) or placebo (n = 120) added to their current regimen of 1 or 2 AEDs. Approximately half of the patients were taking 2 concomitant AEDs at baseline. Target doses ranged from 200 to 500 mg/day of LAMICTAL XR based on concomitant AED (target dose =

200 mg for valproate, 300 mg for AEDs not altering plasma lamotrigine, and 500 mg for enzyme-inducing AEDs). The median partial seizure frequency per week at baseline was 2.3 for LAMICTAL XR and 2.1 for placebo.

The primary endpoint was the median percent change from baseline in partial onset seizure frequency during the entire double-blind treatment phase. The median percent reductions in weekly partial onset seizures were 47% in patients treated with LAMICTAL XR and 25% on placebo, a difference that was statistically significant, defined as a 2-sided *p* value ≤0.05.

Figure 2 presents the percentage of patients (X-axis) with a percent reduction in partial seizure frequency (responder rate) from baseline through the entire treatment period at least as great as that represented on the Y-axis. The proportion of patients achieving any particular level of reduction in partial seizure frequency was consistently higher for the group treated with LAMICTAL XR compared with the placebo group. For example, 44% of patients randomized to LAMICTAL XR experienced a 50% or greater reduction in partial seizure frequency, compared with 21% of patients randomized to placebo.

Figure 2. Proportion of Patients by Responder Rate for LAMICTAL XR and Placebo Group (Partial Onset Seizure Study)



16 HOW SUPPLIED/STORAGE AND HANDLING

LAMICTAL XR (lamotrigine) Extended-Release Tablets

25 mg, yellow with a white center, round, biconvex, film-coated tablets printed on one face in black ink with "LAMICTAL" and "XR 25", unit-of-use bottles of 30 with orange caps (NDC 0173-0754-00).

50 mg, green with a white center, round, biconvex, film-coated tablets printed on one face in black ink with "LAMICTAL" and "XR 50", unit-of-use bottles of 30 with orange caps (NDC 0173-0755-00).

100 mg, orange with a white center, round, biconvex, film-coated tablets printed on one face in black ink with "LAMICTAL" and "XR 100", unit-of-use bottles of 30 with orange caps (NDC 0173-0756-00).

200 mg, blue with a white center, round, biconvex, film-coated tablets printed on one face in black ink with "LAMICTAL" and "XR 200", unit-of-use bottles of 30 with orange caps (NDC 0173-0757-00).

300 mg, gray with a white center, caplet-shaped, film-coated tablets printed on one face in black ink with "LAMICTAL" and "XR 300", unit-of-use bottles of 30 with orange caps (NDC 0173-0761-00).

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

25 mg, yellow with a white center, round, biconvex, film-coated tablets printed on one face in black ink with "LAMICTAL" and "XR 25" and 50 mg, green with a white center, round, biconvex, film-coated tablets printed on one face in black ink with "LAMICTAL" and "XR 50"; blisterpack of 21/25-mg tablets and 7/50-mg tablets (NDC 0173-0758-00).

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

50 mg, green with a white center, round, biconvex, film-coated tablets printed on one face in black ink with "LAMICTAL" and "XR 50"; 100 mg, orange with a white center, round, biconvex, film-coated tablets printed on one face in black ink with "LAMICTAL" and "XR 100"; and 200 mg, blue with a white center, round, biconvex, film-coated tablets printed on one face in black ink with "LAMICTAL" and "XR 200"; blisterpack of 14/50-mg tablets, 14/100-mg tablets, and 7/200-mg tablets (NDC 0173-0759-00).

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

25 mg, yellow with a white center, round, biconvex, film-coated tablets printed on one face in black ink with "LAMICTAL" and "XR 25"; 50 mg, green with a white center, round, biconvex, film-coated tablets printed on one face in black ink with "LAMICTAL" and "XR 50"; and 100 mg, orange with a white center, round, biconvex, film-coated tablets printed on one face in black ink with "LAMICTAL" and "XR 100"; blisterpack of 14/25-mg tablets, 14/50-mg tablets, and 7/100-mg tablets (NDC 0173-0760-00).

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See Medication Guide (17.10).

17.1 Rash

Prior to initiation of treatment with LAMICTAL XR, the patient should be instructed that a rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy) may herald a serious medical event and that the patient should report any such occurrence to a physician immediately.

17.2 Suicidal Thinking and Behavior

Patients, their caregivers, and families should be counseled that AEDs, including LAMICTAL XR, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

17.3 Worsening of Seizures

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

17.4 CNS Adverse Effects

Patients should be advised that LAMICTAL XR may cause dizziness, somnolence, and other symptoms and signs of central nervous system (CNS) depression. Accordingly, they should be advised neither to drive a car nor to operate other complex machinery until they have gained sufficient experience on LAMICTAL XR to gauge whether or not it adversely affects their mental and/or motor performance.

17.5 Blood Dyscrasias and/or Acute Multiorgan Failure

Patients should be advised of the possibility of blood dyscrasias and/or acute multiorgan failure and to contact their physician immediately if they experience any signs or symptoms of these conditions *[see Warnings and Precautions (5.3, 5.4)]*.

17.6 Pregnancy

Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy. Patients should be advised to notify their physicians if they intend to breastfeed or are breastfeeding an infant.

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

17.7 Oral Contraceptive Use

Women should be advised to notify their physician if they plan to start or stop use of oral contraceptives or other female hormonal preparations. Starting estrogen-containing oral contraceptives may significantly decrease lamotrigine plasma levels and stopping estrogen-containing oral contraceptives (including the “pill-free” week) may significantly increase lamotrigine plasma levels *[see Warnings and Precautions (5.7), Clinical Pharmacology (12.3)]*.

Women should also be advised to promptly notify their physician if they experience adverse reactions or changes in menstrual pattern (e.g., break-through bleeding) while receiving LAMICTAL XR in combination with these medications.

17.8 Discontinuing LAMICTAL XR

Patients should be advised to notify their physician if they stop taking LAMICTAL XR for any reason and not to resume LAMICTAL XR without consulting their physician.

17.9 Potential Medication Errors

Medication errors involving LAMICTAL have occurred. In particular the names LAMICTAL or lamotrigine can be confused with the names of other commonly used medications. Medication errors may also occur between the different formulations of LAMICTAL. To reduce the potential of medication errors, write and say LAMICTAL XR clearly. Depictions of the LAMICTAL XR Extended-Release Tablets can be found in the Medication Guide. Each LAMICTAL XR tablet has a distinct color and white center, and is printed with "LAMICTAL XR" and the tablet strength. These distinctive features serve to identify the different presentations of the drug and thus may help reduce the risk of medication errors. LAMICTAL XR is supplied in round, unit-of-use bottles with orange caps containing 30 tablets. The label on the bottle includes a depiction of the tablets which further communicates to patients and pharmacists that the medication is LAMICTAL XR and the specific tablet strength included in the bottle. The unit-of-use bottle with a distinctive orange cap and distinctive bottle label features serves to identify the different presentations of the drug and thus may help to reduce the risk of medication errors. **To avoid a medication error of using the wrong drug or formulation, patients should be strongly advised to visually inspect their tablets to verify that they are LAMICTAL XR each time they fill their prescription and to immediately talk to their doctor/pharmacist if they receive a LAMICTAL XR tablet without a white center and without "LAMICTAL XR" and the strength printed on the tablet as they may have received the wrong medication** *[see Dosage Forms and Strengths (3), How Supplied/Storage and Handling (16)]*.

17.10 Medication Guide

A Medication Guide is provided as a separate leaflet accompanying the product. The full text of the Medication Guide is reprinted below.

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GlaxoSmithKline
Research Triangle Park, NC 27709

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