

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

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HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use Hypersensitivity to the drug or its ingredients. (Boxed Warning, 4) LAMOTRIGINE TABLETS safely and effectively. See full prescribing information for LAMOTRIGINE TABLETS. LAMOTRIGINE tablets, for oral use Initial U.S. Approval: 1994

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

Cases of life-threatening serious rashes, including Stevens-Johnson syndrome and toxic enidermal 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

 exceeding recomm ended initial dose of lamotrigine exceeding recommended dose escalation for lamotrigine. not possible to predict which rashes will prove to be serious or life threatening. Lamotrigine should be discontinued at the

coadministration with valproate.

----RECENT MAJOR CHANGES--Warnings and Precautions, Cardiac Rhythm and Conduction ----INDICATIONS AND USAGE-----

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

Conversion to monotherapy-See Table 4. (2.3)

FULL PRESCRIBING INFORMATION: CONTENTS*

-----DOSAGE FORMS AND STRENGTHS--

2.3 Epilepsy—Conversion from Adjunctive Therapy to

Serious Skin Rashes [see Boxed Warning]

Suicidal Behavior and Ideation

Multiorgan Hypersensitivity Reactions and Orgai Cardiac Rhythm and Conduction Abnormalities

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

WARNING: SERIOUS SKIN RASHES

DOSAGE AND ADMINISTRATION

DOSAGE FORMS AND STRENGTHS

WARNINGS AND PRECAUTIONS

INDICATIONS AND USAGE

first sign of rash, unless the rash is clearly not drug related.

Tatents with Hepatic Impairment is limited. Based on a clinical pharmacology study in 24 subjects with mild, moderate, and findings, lamotrigine tablets could cause serious arrhythmias and/or death in patients with certain underlying cardiac disorders or arrhythmias. Any expected or observed benefit of lamotrigine tablets in an individual patient with clinically important structural or functional heart disease must be carefully weighed against the risk for serious arrhythmias and/or death for that patient. (5.4)

Blood dyscrasias (e.g., neutropenia, thrombocytopenia, pancytopenia): May occur, either with or without an associated hypersensitivity syndrome. Monitor for signs of anemia, unexpected infection, or bleeding. (5.5)

Suicidal behavior and ideation: Monitor for suicidal thoughts or behaviors. (5.6)

 veriaviors. (5.0)
 Aseptic meningitis: Monitor for signs of meningitis. (5.7)
 Medication errors due to product name confusion: Strongly advise patients to visually inspect tablets to verify the received drug is correct. (5.8, 16, 17) If a decision is made to discontinue therapy with lamotrigine tablets, 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 (5.10)]. -----ADVERSE REACTIONS-----

--CONTRAINDICATIONS---

• generalized sezures of Lemina-Gastata syndromic (1...)

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

<u>Epilepsy: Most common adverse reactions (incidence ≥10%) in adults were dizziness, headache, diplopia, ataxia, nausea, blurred vision, somnolence, rhinitis, pharyngitis, and rash. Additional adverse reactions (incidence ≥10%) reported in children included vomiting, infection, fever, accidental injury, diarrhea, abdominal partial-one in the common adverse reactions (incidence ≥10%) in adults were dizziness, headache, diplopia, ataxia, nausea, blurred vision, somnolence, rhinitis, pharyngitis, and rash. Additional adverse reactions (incidence ≥10%) in adults were dizziness, headache, diplopia, ataxia, nausea, blurred vision, somnolence, rhinitis, pharyngitis, and rash. Additional adverse reactions (incidence ≥10%) in adults were dizziness, headache, diplopia, ataxia, nausea, blurred vision, somnolence, rhinitis, pharyngitis, and rash. Additional adverse reactions (incidence ≥10%) in adults were dizziness, headache, diplopia, ataxia, nausea, blurred vision, somnolence, rhinitis, pharyngitis, and rash. Additional adverse reactions (incidence ≥10%) in adults were dizziness, headache, diplopia, ataxia, nausea, blurred vision, somnolence, rhinitis, pharyngitis, and rash. Additional adverse reactions (incidence ≥10%) in adults were dizziness, headache, diplopia, ataxia, nausea, blurred vision, somnolence, rhinitis, pharyngitis, and rash. Additional adverse reactions (incidence ≥10%) reported in children incidence ≥10% in adults were dizziness, headache, diplopia, ataxia, nausea, blurred vision, somnolence, rhinitis, pharyngitis, and rash. Additional adverse reactions (incidence ≥10%) reported in children incidence ≥10% in adults were dizziness, headache, diplopia, ataxia, nausea, blurred vision, somn</u> Bipolar disorder: Maintenance treatment of bipolar I disorder to pain, and tremor. (6.1) delay the time to occurrence of mood episodes with standard therapy. (1.2)

Limitations of Use: Treatment of acute manic or mixed episodes is

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

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

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

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

This section provides specific dosing recommendations for patients older than 12 years and patients aged 2 to 12 years. Within each of these

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

To report SUSPECTED ADVERSE REACTIONS, contact Torrent pharma Inc. at 1-800-FDA-1088 or parties of the commendations are provided depending upon concomitant AEDs or other concomitant medications (see Table Pharma Inc. at 1-800-FDA-1088 or parties older than 12 years and Table 2 for patients older than 12 years. Within each of these age-groups, specific dosing recommendations are provided depending upon concomitant AEDs or other concomitant medications (see Table Pharma Inc. at 1-800-FDA-1088 or patients older than 12 years and Table 2 for patients older than 12 years and Table 2 for patients older than 12 years and Table 2 for patients aged 2 to 12 years.

Dosing is based on concomitant medications, indication, and patient age. (2.1, 2.2, 2.3, 2.4) -----DRUG INTERACTIONS-----Patients Older than 12 Years Valproate increases lamotrigine concentrations more than 2-fold. patient age. (2.1, 2.2, 2.3, 2.4)

• To avoid an increased risk of rash, the recommended initial dose accalations should not be exceeded.

• Carbamazepine, phenytoin, phenobarbital, primidone, and subsequent dose escalations should not be exceeded.

• Carbamazepine, phenytoin, phenobarbital, primidone, and approximately to a proximately to the primitive concentrations by approximately to the primitive concentrations of the primitive concentrations are consistent to the primitive concentrations of the primitive concentrations are consistent to the primitive concentration are consistent to the primit To avoid an increased risk of rash, the recommended initial dose and subsequent dose escalations should not be exceeded. Lamotrigine Tablets Starter Kits are available for the first 5 weeks of treatment. (2.1, 16) Do not restart lamotrigine tablets in patients who discontinued due to rash unless the potential benefits clearly outweigh the risks. (2.1, 5.1) Adjustments to maintenance doses will be necessary in most patients starting or stopping estrogen-containing oral contraceptives. (2.1, 5.9) Protease inhibitors injoinavir rand atazanavir/lopinavir decrease lamotrigine exposure by approximately 50%. (7, 12.3) estrogen-containing oral contraceptives decrease lamotrigine concentrations by approximately 50%. (7, 12.3) estrogen-containing oral contraceptives decrease lamotrigine concentrations by approximately 50%. (7, 12.3) estrogen-containing oral contraceptives decrease lamotrigine concentrations by approximately 50%. (7, 12.3) estrogen-containing oral contraceptives decrease lamotrigine concentrations by approximately 50%. (7, 12.3) estrogen-containing oral contraceptives decrease lamotrigine concentrations by approximately 50%. (7, 12.3) estrogen-containing oral contraceptives decrease lamotrigine exposure by approximately 50%. (7, 12.3) estrogen-containing oral contraceptives decrease lamotrigine exposure by approximately 50%. (7, 12.3) estrogen-containing oral contraceptives decrease lamotrigine exposure by approximately 50%. (7, 12.3) estrogen-containing oral contraceptives decrease lamotrigine concentrations by approximately 50%. (7, 12.3) estrogen-containing oral contraceptives decrease lamotrigine exposure by approximately 50%. (7, 12.3) estrogen-containing oral contraceptives decrease lamotrigine exposure by approximately 50%. (7, 12.3) estrogen-containing oral contraceptives decrease lamotrigine concentrations by approximately 50%. (7, 12.3) estrogen-containing oral contraceptives decrease lamotrigine exposure by approximately 50% and 32%, respectively. (7, 12.3) estrogen-containing oral contraceptiv Discontinuation: Taper over a period of at least 2 weeks -----USE IN SPECIFIC POPULATIONS-----(approximately 50% dose reduction per week). (2.1, 5.10)

 Pregnancy: Based on animal data may cause fetal harm. (8.1)
 Hepatic impairment: Dosage adjustments required in patients with moderate and severe liver impairment. (2.1, 8.6)
 Renal impairment: Reduced maintenance doses may be effective for patients with significant renal impairment. (2.1, 8.7) Adjunctive therapy-See Table 1 for patients older than 12 years and Tables 2 and 3 for patients aged 2 to 12 years. (2.2) See 17 for PATIENT COUNSELING INFORMATION and Medication · Tablets: 25 mg, 100 mg, 150 mg, and 200 mg; scored. (3.1, 16)

6.3 Postmarketing Experience

0.1 Human Overdose Experienc

10.2 Management of Overdose DESCRIPTION

B USE IN SPECIFIC POPULATIONS

Pediatric Use

8.5 Geriatric Use

8.6 Hepatic Impairment 8.7 Renal Impairment 10 OVERDOSAGE

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13 NONCLINICAL TOXICOLOGY

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5.10 Withdrawal Seizures
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5.12 Sudden Unexplained Death in Epilepsy (SUDEP)
5.13 Addition of Lamotrigine Tablets to a Multidrug Regimen
that Includes Visitoriate
that Includes V

Lamotrigine can cause serious rashes requiring hospitalization and discontinuation of treatment. The incidence of these rashes, which have included Stevens-Johnson syndrome, is approximately 0.3% to 0.8% in pediatric patients (aged 2 to 17 years) and

0.08% to 0.3% in adults receiving lamotrigine. One rash-related death was reported in a prospectively followed cohort of 1,983

pediatric patients (aged 2 to 16 years) with epilepsy taking lamotrigine as adjunctive therapy. In worldwide postmarketing experience, rare cases of toxic epidermal necrolysis and/or rash-related death have been reported in adult and pediatric patients.

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

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

Although benign rashes are also caused by lamotrigine, it is not possible to predict reliably which rashes will prove to be serious or life threatening. Accordingly, lamotrigine should ordinarily be discontinued at the first sign of rash, unless the rash is clearly not drug related. Discontinuation of treatment may not prevent a rash from becoming life threatening or permanently disabling or

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

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

Lamotrigine tablets are indicated for the maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes

(depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy [see Clinical Studies

primidone, rifampin, estrogen-containing oral contraceptives, and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonav Valproate inhibits glucuronidation. For dosing considerations for lamotrigine in patients on estrogen-containing contraceptives are atazanavir/ritonavir, see below and Table 13. For dosing considerations for lamotrigine in patients on other drugs known to induce or inhib glucuronidation, see Tables 1, 2, 5-6, and 13.

concomitant AED or other concomitant medications (see Tables 1, 5, and 7). See below for adjustments to maintenance doses of lamotrigine

primidone, or other drugs such as rifampin and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir that induce lamotrigine

olucuronidation [see Drug Interactions (7), Clinical Pharmacology (12.3)], the maintenance dose of lamotrigine will in most cases need to be

(2) Starting Estrogen-Containing Oral Contraceptives: In women taking a stable dose of lamotrigine tablets and not taking carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin and the protease inhibitors lopinavir/ritonavir and

atazanavir/ritonavir that induce lamotrigine glucuronidation *(see Drug Interactions (7), Clinical Pharmacology (12.3)),* the maintenance dose will in most cases need to be increased by as much as 2-fold to maintain a consistent lamotrigine plasma level. The dose increases should

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,

ncreased by as much as 2-fold over the recommended target maintenance dose to maintain a consistent lamotrigine plasma level.

(1) Taking Estrogen-Containing Oral Contraceptives: In women not taking carbamazepine, phenytoin, phenobarbital,

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

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

5.14 Binding in the Eye and Other Melanin-Containing Tissues information are not listed.

but their numbers are too few to permit a precise estimate of the rate.

disfiguring [see Warnings and Precautions (5.1)].

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

DOSAGE AND ADMINISTRATION

important that the dosing recommendations be followed closely.

Target Plasma Levels for Patients with Epilepsy or Bipolar Disorder

Women Taking Estrogen-Containing Oral Contraceptives

in women taking estrogen-containing oral contraceptives

2.1 General Dosing Considerations

INDICATIONS AND USAGE

1.1 Epilepsy

Adjunctive Therapy

Monotherapy

· partial-onset seizures.

2 or more concomitant AEDs.

1.2 Bipolar Disorder

DRUG INTERACTIONS

nesis. Impairment of Fertility

*Sections or subsections omitted from the full prescribing

own to inhibit glucuronidation and decrease the apparent clearance of lamotrigine [see Drug Interactions (7), Clinical 6.1 Clinical Trial Experience
 6.2 Other Adverse Reactions Observed in All Clinical Trials recommendations for oral contraceptives and the protease inhibitor atazanavir/ritonavir can be found in General Dosing Considerations

Weeks 3 and 4

Week 5 onwar

on concomitant valproate is provided in Table 3.

In Patients TAKING

25 mg every other day

25 mg every day

Increase by 25 to

100 to 200 mg/day

100 to 400 mg/day with

that induce glucuronidation

(in 1 or 2 divided doses

valproate and other drugs

50 mg/day every 1 to 2 weeks

[see Dosage and Administration (2.1)]. Patients on rifampin and the protease inhibitor lopinavir/ritonavir should follow the same dosing hospitalized. n/maintenance regimen used with antiepileptic drugs that induce glucuronidation and increase clearance [see Dosage and Patients with History of Allergy or Rash to Other Antiepileptic Drugs Administration (2.1), Drug Interactions (7), Clinical Pharmacology (12.3)]. Patients Aged 2 to 12 Years Recommended dosing guidelines are summarized in Table 2.

Lower starting doses and slower dose escalations than those used in clinical trials are recommended because of the suggestion that the risk of rash may be decreased by lower starting doses and slower dose escalations. Therefore, maintenance doses will take longer to reach in clinical practice than in clinical trials. It may take several weeks to months to achieve an individualized maintenance dose. Maintenance doses in patients ing <30 kg, regardless of age or concomitant AED, may need to be increased as much as 50%, based on clinical response Table 2. Escalation Regimen for Lamotrigine in Patients Aged 2 to 12 Years with Epilepsy

In Patients NOT TAKING

Carbamazepine, Phenytoin,

Phenobarbital, Primidoneb.

25 ma every da

50 mg/day

Increase by 50 mg/day every

225 to 375 mg/day

Carbamazepine, Phenytoin, Phenobarbital, or Primidone^b

and NOT TAKING Valproate

50 mg/day

100 mg/da

in 2 divided dos

Increase by

00 mg/day every 1 to 2 weeks.

300 to 500 mg/day

	In Patients TAKING Valproate ^a	In Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone ^b , or Valproate ^a	In Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone ^a and NOT TAKING Valproate ^a
Weeks 1 and 2	0.15 mg/kg/day in 1 or 2 divided doses, rounded down to the nearest whole tablet (see Table 3 for weight-based dosing guide)	0.3 mg/kg/day in 1 or 2 divided doses, rounded down to the nearest whole tablet	0.6 mg/kg/day in 2 divided doses, rounded down to the nearest whole tablet
Weeks 3 and 4	0.3 mg/kg/day in 1 or 2 divided doses, rounded down to the nearest whole tablet (see Table 3 for weight-based dosing guide)	0.6 mg/kg/day in 2 divided doses, rounded down to the nearest whole tablet	1.2 mg/kg/day in 2 divided doses, rounded down to the nearest whole tablet
Week 5 onward to maintenance	The dose should be increased every 1 to 2 weeks as follows: calculate 0.3 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily dose.	The dose should be increased every 1 to 2 weeks as follows: calculate 0.6 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily dose.	The dose should be increased every 1 to 2 weeks as follows: calculate 1.2 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily dose.
Usual maintenance dose	1 to 5 mg/kg/day (maximum 200 mg/day in 1 or 2 divided doses) 1 to 3 mg/kg/day with valproate alone	4.5 to 7.5 mg/kg/day (maximum 300 mg/day in 2 divided doses)	5 to 15 mg/kg/day (maximum 400 mg/day in 2 divided doses)
Maintenance dose in patients	May need to be increased by as much as 50%, based on	May need to be increased by as much as 50%, based on	May need to be increased by as much as 50%, based on

clinical response. clinical response. Note: Only whole tablets should be used for dosing Drugs that induce lamotrigine glucuronidation and increase clearance, other than the specified antiepileptic drugs, include 5.6 Suicidal Behavior and Ideation

estrogen-containing oral contraceptives, rifampin, and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir. Dosing recommendations for oral contraceptives and the protease inhibitor atazanavir/ritonavir can be found in General Dosing Considerations [see Dosage and Administration (2.1)]. Patients on rifampin and the protease inhibitor lopinavir/ritonavir should follow the same dosing titration/maintenance regimen used with antiepileptic drugs that induce glucuronidation and increase clearance [see Dosage and Administration (2.1), Drug Interactions (7), Clinical Pharmacology (12.3)]. Administration (2.1), Drug Interactions (7), Clinical Pharmacology (12.3)]

Table 3. The Initial Weight-Based Dosing Guide for Patients Aged 2 to 12 Years Taking Valproate (Weeks 1 to 4) with Epilepsy Give this daily dose, using the most appropriate combination of lamotrigine

And less than Weeks 1 and 2 5 mg every da <u> Jsual Adjunctive Maintenance Dose for Epilepsy</u>

The usual maintenance doses identified in Tables 1 and 2 are derived from dosing regimens employed in the placebo-controlled adjunctive trials in which the efficacy of lamotrigine tablets was established. In patients receiving multidrug regimens employing carbama phenytoin, phenobarbital, or primidone without valproate, maintenance doses of adjunctive lamotrigine tablets as high as 700 mg/day have been used. In patients receiving <u>valproate alone</u>, maintenance doses of adjunctive lamotrigine tablets as high as 200 mg/day have been used. The advantage of using doses above those recommended in Tables 1 to 4 has not been established in controlled trials. reatment of acute manic or mixed episodes is not recommended. Effectiveness of lamotrigine tablets in the acute treatment of mood 2.3 Epilepsy—Conversion from Adjunctive Therapy to Monotherapy

The goal of the transition regimen is to attempt to maintain seizure control while mitigating the risk of serious rash associated with the rapid titration of lamotrigine tablets. The recommended maintenance dose of lamotrigine tablets as monotherapy is 500 mg/day given in 2 divided doses. There are suggestions, yet to be proven, that the risk of severe, potentially life-threatening rash may be increased by (1) coadministration of lamotrigine tablets with valproate, (2) exceeding the recommended initial dose of lamotrigine tablets, or (3) exceeding the recommended dose escalation for lamotrigine tablets. However, cases have occurred in the absence of these factors [see Boxed Warning]. Therefore, it is insented that the design extensive the factors are presented to the property of the proper To avoid an increased risk of rash, the recommended initial dose and subsequent dose escalations for lamotrigine tablets should not be

exceeded [see Boxed Warning] 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.

teatment, based upon concomitant medications, for patients with epilepsy (older than 12 years) and bipolar I disorder (adults) and are intended to help reduce the potential for rash. The use of lamotrigine Starter Kits is recommended for appropriate patients who are starting.

Conversion from Adjunctive Therapy with Valproate to Monotherapy with Lamotrigine Tablets. The conversion regimen involves the 4 steps outlined in Table 4. The conversion regimen involves the 4 steps outlined in Table 4.

or restarting lamotrigine [see How Supplied/Storage and Handling (16)].	The conversio	n regimen involves the 4 steps outlined in Table 4.		
It is recommended that lamotrigine tablets not be restarted in patients who discontinued due to rash associated with prior treatment with lamotrigine unless the potential benefits clearly outweigh the risks. If the decision is made to restart a patient who has discontinued	Epilepsy	ersion from Adjunctive Therapy with Valproate to Monot	herapy with Lamotrigine in Patients Aged 16 Years and Older with	i i
lamotrigine tablets, the need to restart with the initial dosing recommendations should be assessed. The greater the interval of time since the		Lamotrigine Tablets	Valproate	5
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)).		Achieve a dose of 200 mg/day according to guidelines in Table 1.	Maintain established stable dose.	T
Lamotrigine Added to Drugs Known to Induce or Inhibit Glucuronidation	Step 2	Maintain at 200 mg/day.	Decrease dose by decrements no greater than 500 mg/day/week to 500 mg/day and then maintain for 1 week.	F
Because lamotrigine is metabolized predominantly by glucuronic acid conjugation, drugs that are known to induce or inhibit glucuronidation may affect the apparent clearance of lamotrigine. Drugs that induce glucuronidation include carbamazepine, phenytoin, phenobarbital primidone, rifampin, estrogen-containing oral contraceptives, and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir	Step 3	Increase to 300 mg/day and maintain for 1 week.	Simultaneously decrease to 250 mg/day and maintain for 1 week.	a
Valproate inhibits glucuronidation. For dosing considerations for lamotrigine in patients on estrogen-containing contraceptives and atazanavir/ritonavir, see below and Table 13. For dosing considerations for lamotrigine in patients on other drugs known to induce or inhibit	Step 4	Increase by 100 mg/day every week to achieve maintenance dose of 500 mg/day.	Discontinue.	F n €

A therapeutic response (see Clinical Pharmacology (12.3)].

No specific dosing guidelines can be provided for conversion to monotherapy with lamotrigine tablets with AEDs other than carbamazepine, phenytoin, phenobarbital, primitione, or valproate. The goal of maintenance treatment with lamotrigine is to delay the time to occurrence of mood episodes (depression, mania, hypomania,

Starting Lamotrigine Tablets in Women Taking Estrogen-Containing Oral Contraceptives: Although 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 mixed episodes) in patients treated for acute mood episodes with standard therapy [see Indications and Usage (1.2)]. dose-escalation guidelines for lamotrigine should be necessary solely based on the use of estrogen-containing oral contraceptives. Therefore, dose escalation should follow the recommended guidelines for initiating adjunctive therapy with lamotrigine tablets based on the The target dose of lamotrigine tablets is 200 mg/day (100 mg/day in patients taking valproate, which decreases the apparent clearance of should be strongly advised to visually inspect their tablets to verify that they are lamotrigine, as well as the correct formulation of lamotrigine,

> drugs such as rifampin and the protease inhibitor lopinavir/ritonavir that increase the apparent clearance of lamotrigine). In the clinical trials, 5.9 Concomitant Use with Oral Contraceptives doses up to 400 mg/day as monotherapy were evaluated; however, no additional benefit was seen at 400 mg/day compared with 200 mg/day [see Clinical Studies (14.2)]. Accordingly, doses above 200 mg/day are not recommended. Treatment with lamotrigine tablets is introduced, based on concurrent medications, according to the regimen outlined in Table 5. If other psychotropic medications are withdrawn following stabilization, the dose of lamotrigine tablets should be adjusted. In patients discontinuing valproate, the dose of lamotrigine tablets should be doubled over a 2-week period in equal weekly increments (see Table 6). In patients

discontinuing carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin and the protease inhibitors 5.10 Withdrawal Seizures will in most cases need to be increased by as much as 2-fold to maintain a consistent lamotrigine plasma level. The dose increases should not be abruptly discontinued. In patients with epilepsy there is a possibility of increasing seizure the first week and then should be decreased by half over a 2-week period in equal weekly decrements (see Table 6). The dose of lamotrigine glucuronidation, the dose of lamotrigine plasma levels or any them the first week and then should be decreased by half over a 2-week period in equal weekly decrements (see Table 6). The dose of lamotrigine plasma levels or lamotrigine plasma levels or a distribution of the commended rate (see Table 1 and 5) unless lamotrigine plasma levels or lamotrigine plasma levels or lamotrigine plasma levels or look and the same time that the oral contraceptive is introduced and continue, based on clinical response, no more rapidly than 50 to 100 lines and the same time that the oral contraceptive is introduced and continue, based on clinical response, no more rapidly than 50 to 100 lines are lamotrigine plasma levels or lamotrigine plasma le mg/day every week. Dose increases should not exceed the recommended rate (see Tables 1 and 5) unless lamotrigine plasma levels or clinical response support larger increases. Gradual transient increases in lamotrigine plasma levels may occur during the week of inactive If other drugs are subsequently introduced, the dose of lamotrigine tablets may need to be adjusted. In particular, the introduction of

valproate requires reduction in the dose of lamotrigine [see Drug Interactions (7), Clinical Pharmacology (12.3)]. and diplopia. If adverse reactions attributable to lamotrigine tablets consistently occur during the pill-free week, dose adjustments to the

overall maintenance dose may be necessary. Dose adjustments limited to the pill-free week are not recommended. For women taking lamotrigine tablets in addition to carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin and the protease	[see Boxed Warning]. Table 5. Escalation F	Regimen for Lamotrigine Tablets	in Adults with Bipolar Disorder	·	t t
inhibitors lopinavir/ritonavir and atazanavir/ritonavir that induce lamotrigine glucuronidation <i>[see Drug Interactions (7), Clinical Pharmacology (12.3)]</i> , no adjustment to the dose of lamotrigine tablets should be necessary. (3) Stopping Estrogen-Containing Oral Contraceptives: In women not taking carbamazepine, phenytoin, phenobarbital,		In Patients TAKING	In Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital. Primidone ^b . or	In Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone ⁶ and	
primidone, or other drugs such as rifampin and the protease inhibitors lopinavil/ritonavir and atazanavir/ritonavir that induce lamotrigine glucuronidation [see Drug Interactions (7), Clinical Pharmacology (12.3)], the maintenance dose of lamotrigine will in most cases need to be		Valproate ^a 25 mg every <i>other</i> day	Valproate ^a 25 mg daily	NOT TAKING Valproate ^a 50 mg daily	١
decreased by as much as 50% in order to maintain a consistent lamotrigine plasma level. The decrease in dose of lamotrigine tablets should not exceed 25% of the total daily dose per week over a 2-week period, unless clinical response or lamotrigine plasma levels indicate	Weeks 3 and 4	25 mg daily	50 mg daily	100 mg daily, in divided doses	1
otherwise [see Clinical Pharmacology (12.3)]. In women taking lamotrigine in addition to carbamazepine, phenytoin, phenobarbital,	Week 5	50 mg daily	100 mg daily	Zoo mg dany, in divided doses	(

primidone, or other drugs such as rifampin and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir that induce lamotrigine glucuronidation [see Drug Interactions (7), Clinical Pharmacology (12.3)], no adjustment to the dose of lamotrigine tablets should be

recommendations for oral contraceptives and the protease inhibitor atazanavir/fritonavir can be found in General Dosing Considerations [see Dosage and Administration (2.1)]. Patients on rifampin and the protease inhibitor lopinavir/ritonavir should follow the same dosing trattation/maintenance regimen used with antiepileptic drugs that induce glucuronidation and increase clearance [see Dosage and Administration (2.1), Drug Interactions (7), Clinical Pharmacology (12.3)].

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 administration (2.1), Drug Interactions (7), Clinical Pharmacology (12.3)].

Hypersensitivity to the drug or its ingredients. (Boxed Warning, 4) ***Hypersensitivity to the drug or its ingredients. (Boxed Warning, 4) ***Life-threatening serious rash and/or rash-related death Discontinue at the first sign of rash, unless the rash is clearly not drug related. (Boxed Warning, 5.1) **Hemophagocytic lymphohisticoytosis: Consider this diagnosis and evaluate patients immediately if they develop signs or any evaluate and evaluate patients immediately if they develop signs or any evaluated	rease clearance, other than the	
Life-threatening serious rash and/or rash-related death: Discontinue at the first sign of rash, unless the rash is clearly not drug related. (Boxed Warning, 5.1) Hemophagocytic lymphohisticoytosis: Consider this diagnosis and evaluate patients immediately if they develop signs or and evaluate patients immediately if they develop signs or and evaluate not the disagree of lamotrigine plasma levels. Therefore, adjustments to the dosage of lamotrigine tablets in estrogen-containing oral contraceptives, rifampin, and the progestin-only pills had no effect on lamotrigine plasma levels. Therefore, adjustments to the dosage of lamotrigine tablets in estrogen-containing oral contraceptives, rifampin, and the progestin-only pills had no effect on lamotrigine plasma levels. Therefore, adjustments to the dosage of lamotrigine tablets in estrogen-containing oral contraceptives, rifampin, and the progestin-only pills had no effect on lamotrigine plasma levels. Therefore, adjustments to the dosage of lamotrigine tablets in estrogen-containing oral contraceptives, rifampin, and the progestin-only pills had no effect on lamotrigine plasma levels. Therefore, adjustments to the dosage of lamotrigine tablets in estrogen-containing oral contraceptives, rifampin, and the progestin-only pills had no effect on lamotrigine plasma levels. Therefore, adjustments to the dosage of lamotrigine tablets in estrogen-containing oral contraceptives, rifampin, and the progestin-only pills had no effect on lamotrigine plasma levels. Therefore, adjustments to the dosage of lamotrigine tablets in the progestin-only pills had no effect on lamotrigine plasma levels. Therefore, adjustments to the dosage of lamotrigine tablets in the progestin-only pills had no effect on lamotrigine plasma levels. Therefore, adjustments to the dosage of lamotrigine tablets in the progestin-only pills had no effect on lamotrigine plasma levels. Therefore, adjustments to the dosage of lamotrigine tablets in the progestin-only pills had no effect on lamotrigi	rease the apparent clearance of lame	otrigine [see Drug Interactions (7), Clinic
Discontinue at the first sign of rash, unless the rash is clearly not drug related. (Boxed Warning, 5.1) Hemophagocytic lymphohisticoytosis: Consider this diagnosis and evaluate patients immediately if they develop signs or	rease clearance, other than the	
drug related. (Boxed Warning, 5.1) The effect of other hormonal contraceptive preparations or hormone replacement therapy on the pharmacokinetics of lamotrigine has not Hemophagocytic lymphohisticocytosis: Consider this diagnosis been systematically evaluated. It has been reported that ethinylestradiol, not progestogens, increased the clearance of lamotrigine up to brugs that induce lamotrigine glucuronidation and in 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 brugs that induce lamotrigine glucuronidation and in contraceptive preparations or hormone replacement therapy on the pharmacokinetics of lamotrigine has not brugs that induce lamotrigine glucuronidation and in contraceptive preparations or hormone replacement therapy on the pharmacokinetics of lamotrigine has not brugs that induce lamotrigine alone and in contraceptive preparations or hormone replacement therapy on the pharmacokinetics of lamotrigine has not brugs that induce lamotrigine alone induced in the pharmacokinetics of lamotrigine has not brugs that induce lamotrigine alone induced in the pharmacokinetics of lamotrigine has not brugs that induce lamotrigine alone in the pharmacokinetics of lamotrigine has not brugs that induce lamotrigine alone in the pharmacokinetics of lamotrigine has not brugs that induce lamotrigine has no		
Hemophagocytic lymphohisticocytosis: Consider this diagnosis been systematically evaluated. It has been reported that ethinylestradiol, not progestogens, increased the clearance of lamotrigine up to and evaluate patients immediately if they develop signs or 2-fold, and the progestin-only pills had no effect on lamotrigine plasma levels. Therefore, adjustments to the dosage of lamotrigine tablets in estrogen-containing oral contraceptives, rifampin, and it		
and evaluate patients immediately if they develop signs or 2-fold, and the progestin-only pills had no effect on lamotrigine plasma levels. Therefore, adjustments to the dosage of lamotrigine tablets in estrogen-containing oral contraceptives, mampin, and the		
symptoms of systemic inflammation. Discontinue lamotrigine the presence of progestogens alone will likely not be needed. recommendations for oral contraceptives and the protease tablets if an alternative etiology is not established. (5.2) Reflects Taking Assessmit/Discontinue Reflects Taking Assessmit Ass		
tablets if an alternative etiology is not established. (5.2) Fatal or life-threatening hypersensitivity reaction: Multiorgan titration/maintenance regimen used with antiepileptic dru		
is hypersensitivity reactions, also known as drug reaction with While atazanavir/ritonavir does reduce the lamotrigine plasma concentration, no adjustments to the recommended dose-escalation Administration (2.1), Drug Interactions (7), Clinical Pharmac		in mercase cicarance [see bosage ar
e. eosinophilia and systemic symptoms, may be fatal or guidelines for lamotrigine tablets should be necessary solely based on the use of atazanavir/ritonavir. Dose escalation should follow the	05 (//	lowing Discontinuation of Davehatron
III IIII Ulleatening. Early signs may include fash, lever, and recommended guidelines for initiating adjunctive therapy with lamoungine based on concomitant medications (see	Addits with bipolar disorder for	iowing discontinuation of esychotrop
in Tyliphadoliopadily. Higgs reactions may be associated with other tradics 1, 2, and 3). In patients already axing maintenance doses of almost girls axing globarolindation inducers, the dose of		Attau Discontinuation of
organ involvement, such as hepatitis, hepatic failure, blood lamotrigine tablets may need to be increased if atazanavir/ritonavir is added or decreased if atazanavir/ritonavir is discontinued [see Clinical dyscrasias, or acute multiorgan failure. Lamotrigine tablets Pharmacology (12.3)].		After Discontinuation of
should be disceptinued if alternate aticles of this reaction is not	After Discontinuation	Carbamazepine,
p found. (5.3)		Phenytoin, Phenobarbital, or
• Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction abnormalities: Based on in vitro • Cardiac rhythm and conduction	of Valproate ^a	Primidone ^b
ie minings, famotrigino tabloto control attrivamento control attrivamento control attrivamento control attriv	Current Dose of Lamotrigine Tablets (mg/day	Current Dose of Lamotrigine Tablets
and/or death in patients with certain underlying cardiac disorders be made. No dosage adjustment is needed in patients with mild liver impairment. Initial, escalation, and maintenance doses should generally or arrhythmias. Any expected or observed benefit of lamotriqine be reduced by approximately 25% in patients with moderate and severe liver impairment without ascites and 50% in patients with severe liver Primidone*)	100 trigine lablets (mg/da)	(mg/day)
tablete in an individual nations with alignostly important structural impoirment with assistance Togaletian and maintenance decay may be adjusted according to alignost repense.		400
4. or functional heart disease must be corofully waighed against the	lets 150	400
risk for serious arrhythmias and/or death for that patient. (5.4) Week 2 Maintain current dose of Lamotrigine Tal	lets 200	300
Blood dyscrasias (e.g., neutropenia, thrombocytopenia, Initial doses of lamotrigine should be based on patients' concomitant medications (see Tables 1 to 3, and 5); reduced maintenance doses Week 3 onward Maintain current dose of Lamotrigine Tal Week 3 onward Maintain current dose of Lamotrigine Tal Maintain curren	lets 200	200
pancytopenia): May occur, either with or without an associated may be effective for patients with significant renal impairment [see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]. Few hypersensitivity syndrome. Monitor for signs of anemia, patients with severe renal impairment have been evaluated during chronic treatment with lamotrigine. Because there is inadequate experience a Valoroste has been shown to inhibit allucuronidation and definition and		

Priors that induce lamotrinine glucuronidation and increase clearance, other than the specified antiepilentic drugs include Epilepsy: For patients receiving lamotrigine tablets 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. estrogen-containing oral contraceptives, rifampin, and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir. Dosing recommendations for oral contraceptives and the protease inhibitor atazanavir/ritonavir can be found in General Dosing Considerations Isee Dosage and Administration (2.1)1. Patients on rifampin and the protease inhibitor lopinavir/ritonavir should follow the same dosing | See Dosage and Administration (2.1), Figure 3 of the pilotest implication and increase clearance [see Dosage and Administration (2.1), Drug Interactions (7), Clinical Pharmacology (12.3)].

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

Additional prolong the half-life of lamotrigine; discontinuing all provides should shorten the half-life of lamotrigine. DOSAGE FORMS AND STRENGTHS Bipolar Disorder: In the controlled clinical trials, there was no increase in the incidence, type, or severity of adverse reactions following abrupt 25 mg, White to off white, round shape, flat face beveled edge, uncoated tablets debossed with "45" on one side and break line on other side. termination of lamotrigine tablets. In the clinical development program in adults with bipolar disorder, 2 patients experienced seizures shortly after abrupt withdrawal of lamotrigine tablets. Discontinuation of lamotrigine tablets should involve a step-wise reduction of dose over at 100 mg. White to off white, round shape, flat face beveled edge, uncoated tablets debossed with "1047" on one side and break line on other "100 mg. White to off white, round shape, flat face beveled edge, uncoated tablets debossed with "1047" on one side and break line on other "100 mg. White to off white, round shape, flat face beveled edge, uncoated tablets debossed with "1047" on one side and break line on other "100 mg. White to off white, round shape, flat face beveled edge, uncoated tablets debossed with "1047" on one side and break line on other "100 mg. White to off white, round shape, flat face beveled edge, uncoated tablets debossed with "1047" on one side and break line on other "100 mg. White to off white, round shape, flat face beveled edge, uncoated tablets debossed with "1047" on one side and break line on other "100 mg. White to off white, round shape, flat face beveled edge, uncoated tablets debossed with "1047" on one side and break line on other "100 mg. White to off white, round shape, flat face beveled edge, uncoated tablets debossed with "1047" on one side and break line on other "100 mg. White to off white, round shape, flat face beveled edge, uncoated tablets debossed with "1047" on one side and break line on other "100 mg. White to off white, round shape, flat face beveled edge, uncoated tablets debossed with "1047" on one side and break line on other "100 mg. White to off white, round shape, flat face beveled edge, uncoated tablets debossed with "1047" on one side and break line on other "100 mg. White to off white, round shape, flat face beveled edge, uncoated tablets debossed with "1047" on one side and break line on other "100 mg. White to off white, round shape, flat face beveled edge, uncoated tablets

150 mg, White to off white, round shape, flat face beveled edge, uncoated tablets debossed with "1048" on one side and break line on other 6.1 Clinical Trial Experience

Lamotrigine tablets are contraindicated in patients who have demonstrated hypersensitivity (e.g., rash, angioedema, acute urticaria, extensive pruritus, mucosal ulceration) to the drug or its ingredients [see Boxed Warning, Warnings and Precautions (5.1, 5.3)].

5 WARNINGS AND PRECAUTIONS 5.1 Serious Skin Rashes (see Boxed Warning) Pediatric Population

The incidence of serious rash associated with hospitalization and discontinuation of lamotrigine in a prospectively followed cohort of pediatric patients (aged 2 to 17 years) is approximately 0.3% to 0.8%. One rash-related death was reported in a prospectively followed cohort of 1,983 pediatric patients (aged 2 to 16 years) with epilepsy taking lamotrigine as adjunctive therapy. Additionally, there have been rare cases of toxic epidermal necrolysis with and without permanent sequelae and/or death in U.S. 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 for epilepsy, 1.2% (6 of 482) experienced a serious rash compared

Serious rash associated with hospitalization and discontinuation of lamotrigine occurred in 0.3% (11 of 3,348) of adult patients who receive lamotrigine in premarketing clinical trials of epilepsy. In the bipolar and other mood disorders clinical trials, the rate of serious rash was 0.08% (1 of 1,233) of adult patients who received lamotrigine as initial monotherapy and 0.13% (2 of 1,538) of adult patients who received lamotrigine as adjunctive therapy. No fatalities occurred among these individuals. However, in worldwide postmarketing experience, rare ases 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 those associated

with multiorgan hypersensitivity [see Warnings and Precautions (5.3)]. Trian induce lamotrigine glucuronidation and increase clearance, other than the specified antiepileptic drugs, include Triangt induce lamotrigine glucuronidation and increases the risk of serious, potentially life-threatening rash in adults. estrogen-containing oral contraceptives, rifampin, and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir. Dosing

Specifically, of 584 patients administered lamotrigine 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 lamotrigine in the absence of valproate were

The risk of nonserious rash may be increased when the recommended initial dose and/or the rate of dose escalation for lamotrigine is

exceeded and in patients with a history of allergy or rash to other AEDs. 5.2 Hemophagocytic Lymphohistiocytosis

5.2 Hemophagocytic Lymphohistiocytosis (HLH) has occurred in pediatric and adult patients taking lamotrigine for various indications. HLH is a life-threatening syndrome of pathologic immune activation characterized by clinical signs and symptoms of extreme systemic inflammation. It is associated with high mortality rates if not recognized early and treated. Common findings include fever, hepatosplenomegaly, rash, lymphadenopathy, neurologic symptoms, cytopenias, high serum ferrittin, hypertriglyceridemia, and liver function and coagulation abnormalities. In cases of HLH reported with lamotrigine, patients have presented with signs of systemic inflammation (fever, rash, hepatosplenomegaly, and organ system dysfunction) and blood dyscrasias. Symptoms have been reported to occur within 8 to 24 days following the initiation of treatment. Patients who develop early manifestations of pathologic immune activation should be evaluated immediately, and a diagnosis of HLH should be considered. Lamotrigine should be discontinued if an alternative etiology for the signs or symptoms cannot be established. symptoms cannot be established.

5.3 Multiorgan Hypersensitivity Reactions and Organ Failure Multiorgan hypersensitivity reactions, also known as drug reaction with eosinophilia and systemic symptoms (DRESS), have occurred with amotrigine. Some have been fatal or life threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or nathy in association with other organ system involvement, such as benatitis, penbritis, bematologic abnormalities, myocarditi r myositis, sometimes resembling an acute viral infection. Eosinophilia is often present. This disorder is variable in its expression, and othe atalities associated with acute 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 lamotrigine in epilepsy clinical trials. Rare fatalities from multiorgan failure have also been reported Isolated liver failure without rash or involvement of other organs has also been reported with lamotrigine It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even though a rash is not If such signs or symptoms are present, the patient should be evaluated immediately. Lamotrigine should be discontinued if an

alternative etiology for the signs or symptoms cannot be established. (e.g., fever, lymphadenopathy) may herald a serious medical event and that the patient should report any such occurrence to a healthcare

| 5.4 Cardiac Rhythm and Conduction Abnormalities

In vitro testing showed that lamotrigine exhibits Class IB antiarrhythmic activity at therapeutically relevant concentrations [see Clinical Pharmacology (12.2)]. Based on these in vitro findings, lamotrigine could slow ventricular conduction (widen QRS) and induce proarrhythmia, which can lead to sudden death, in patients with clinically important structural or functional heart disease (i.e., patients with heart failure, valvular heart disease, congenital heart disease, conduction system disease, ventricular arrhythmias, cardiac channelopathies [e.g., Brugada syndrome], clinically important ischemic heart disease, or multiple risk factors for coronary artery disease). Any expected or begins of the content of the content

here have been reports of blood dyscrasias that may or may not be associated with multiorgan hypersensitivity (also known as DRESS) [see Valproate has been shown to inhibit glucuronidation and decrease the apparent clearance of lamotrigine [see Drug Interactions (7), Clinical Warnings and Precautions (5.3)]. These have included neutropenia, leukopenia, anemia, thrombocytopenia, pancytopenia, and, rarely, aplastic anemia and pure red cell aplasia

nized to 1 of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI; 1.2, 2.7) of suicidal thinking or behavio compared with 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 with 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

uicidal 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.

zepine. Table 7 shows absolute and relative risk by indication for all evaluated AEDs.

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

Anyone considering prescribing lamotrigine or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated withdrawn by 20% decrements each week over a 4-week period. The regimen for the withdrawal of the concomitant AED is based on Lamotrigine Tablets Starter Kits provide lamotrigine at doses consistent with the recommended titration schedule for the first 5 weeks of the controlled monotherapy clinical trial.

Anyone considering prescribing lamotrigine or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated withdrawn by 20% decrements each week over a 4-week period. The regimen for the withdrawal of the concomitant tenzyme-inducing AED should be withdrawn by 20% decrements each week over a 4-week period. The regimen for the withdrawal of the concomitant tenzyme-inducing AED should be withdrawn by 20% decrements each week over a 4-week period. The regimen for the withdrawal of the concomitant tenzyme-inducing AED should be withdrawn by 20% decrements each week over a 4-week period. The regimen for the withdrawal of the concomitant tenzyme-inducing AED should be withdrawn by 20% decrements each week over a 4-week period. The regimen for the withdrawal of the concomitant tenzyme-inducing AED should be withdrawn by 20% decrements each week over a 4-week period. The regimen for the withdrawn by 20% decrements each week over a 4-week period. The regimen for the withdrawn by 20% decrements each week over a 4-week period. The regimen for the withdrawn by 20% decrements each week over a 4-week period. The regimen for the withdrawn by 20% decrements each week over a 4-week period. The concomitant enzyme-inducing AED should be without the regimen for the withdrawn by 20% decrements each week over a 4-week period. The concomitant enz 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, the emergence of suicidal thoughts or suicidal behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

5.7 Aseptic Meningitis Therapy with lamotrigine increases the risk of developing aseptic meningitis. Because of the potential for serious outcomes of untreated meningitis due to other causes, patients should also be evaluated for other causes of meningitis and treated as appropriate. Postmarketing cases of aseptic meningitis have been reported in pediatric and adult patients taking lamotrigine for various indication Symptoms upon presentation have included headache, fever, nausea, vomiting, and nuchal rigidity. Rash, photophobia, myalgia, chills, altered consciousness, and somnolence were also noted in some cases. Symptoms have been reported to occur within 1 day to one and a half months following the initiation of treatment. In most cases, symptoms were reported to resolve after discontinuation of lamotrigine. Re-exposure resulted in a rapid return of symptoms (from within 30 minutes to 1 day following re-initiation of treatment) that were frequently

Conversion from Adjunctive Therapy with Antiepileptic Drugs other than Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate to Monotherapy with Lamotrigine Tablets

No specific dosing guidelines can be provided for conversion to monotherapy with lamotrigine tablets with AEDs other than carbamazepine, phenytoin, phenobarbital, primidone, or valproate.

So the Primidone of 500 mg/day.

erythematosus or other autoimmune useases.

Cerebrospinal fluid (CSF) analyzed at the time of clinical presentation in reported cases was characterized by a mild to moderate pleocytosis, normal glucose levels, and mild to moderate increase in protein. CSF white blood cell count differentials showed a predominance of lymphocytes was reported in approximately one transported in approximately one transport of the cases, although a predominance of lymphocytes was reported in approximately one transported in approximately one transport of the cases, although a predominance of lymphocytes was reported in approximately one transport of the cases, although a predominance of lymphocytes was reported in approximately one transport of the cases, although a predominance of lymphocytes was reported in approximately one transport of the cases, although a predominance of lymphocytes was reported in approximately one transport of the cases, although a predominance of lymphocytes was reported in approximately one transport of the cases, although a predominance of lymphocytes was reported in approximately one transport of the cases, although a predomin 5.8 Potential Medication Errors

Medication errors involving lamotrigine have occurred. In particular, the name lamotrigine can be confused with the names of other commonly used medications. Medication errors may also occur between the different formulations of lamotrigine. To reduce the potential of medication errors, write and say lamotrigine clearly. Depictions of the lamotrigine tablets can be found in the Medication Guide that accompanies the product to highlight the distinctive markings, colors, and shapes that serve to identify the different presentations of the drug and thus may help reduce the risk of medication errors. To avoid the medication error of using the wrong drug or formulation, patients motrigine, and 400 mg/day in patients not taking valproate and taking either carbamazepine, phenytoin, phenobarbital, primidone, or other each time they fill their prescription.

> 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 therapy, plasma lamotrigine (see Dosage and Administration (2.1)). During the week of inactive hormone preparation (pil-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.

(approximately 50% reduction per week) [see Dosage and Administration (2.1)] 5.11 Status Epilepticus

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) were made. 5.12 Sudden Unexplained Death in Epilepsy (SUDEP)

During the premarketing development of lamotrigine, 20 sudden and unexplained deaths were recorded among a cohort of 4,700 patients with epilepsy (5,747 patient-years of exposure). ome of these could represent seizure-related deaths in which the seizure was not observed, e.g., at night. This represents an incidence of Digestive: Anorexia, dry mouth, rectal hemorrhage, peptic ulcer. O.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 death in epilepsy (SUDEP) in patients 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 is milar to that in the clinical development program for the general population of patients with epilepsy, to 0.004 for a recently studied clinical trial population with the clinical development of patients with epilepsy, to 0.004 for a recently studied clinical trial population of patients with epilepsy. Consequently whether these figures are reassuring or the clinical trial population of patients with epilepsy. Consequently whether these figures are reassuring or the clinical trial population of patients with epilepsy. Consequently whether these figures are reassuring or the clinical trial population of patients with epilepsy. Consequently whether these figures are reassuring or the clinical trial population of patients with epilepsy. Consequently whether these figures are reassuring or the clinical trial population of patients with epilepsy. Consequently whether these figures are reassuring or the clinical trial population of patients with epilepsy. Consequently whether these figures are reassuring or the clinical trial population of patients with epilepsy. Consequently whether these figures are reassuring or the clinical trial population of patients with epilepsy. Consequently whether these figures are reassuring or the clinical trial population of patients.

pment program for 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 with the cohort receiving lamotrigine and the accuracy of Respiratory: Epistaxis, bronchitis, dyspnea the estimates provided. Probably most reassuring is the similarity of estimated SUDEP rates in patients receiving lamotrigine and those Skin and Appendages: Contact dermatitis, dry skin, sweating. Week 7 100 mg daily 200 mg daily up to 400 mg daily, in divided doses

* Valproate has been shown to inhibit glucuronidation and decrease the apparent clearance of lamotrigine [see Drug Interactions (7), Clinical although it certainly does not prove, that the high SUDEP rates reflect population rates, not a drug effect.

* Valproate has been shown to inhibit glucuronidation and decrease the apparent clearance of lamotrigine [see Drug Interactions (7), Clinical although it certainly does not prove, that the high SUDEP rates reflect population rates, not a drug effect. 5.13 Addition of Lamotrigine to a Multidrug Regimen that Includes Valproate

Probability (12.5).

Brugs that induce lamotrigine glucuronidation and increase clearance, other than the specified antiepileptic drugs, include estrogen-containing oral contraceptives, rifampin, and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir an

cause toxicity in these tissues after extended use. Although ophthalmological testing was performed in 1 controlled clinical trial, the testing was inadequate to exclude subtle effects or injury occurring after long-term exposure. Moreover, the capacity of available tests to detect potentially adverse consequences, if any, of lamotrigine's binding to melanin is unknown [see Clinical Pharmacology (12.2)]. Accordingly, although there are no specific recommendations for periodic ophthalmological monitoring, prescribers should be aware of the

possibility of long-term ophthalmologic effects. 5.15 Laboratory Tests False-Positive Drug Test Results

Lamotrigine has been reported to interfere with the assay used in some rapid urine drug screens, which can result in false-positive readings, particularly for phencyclidine (PCP). A more specific analytical method should be used to confirm a positive result. Plasma Concentrations of Lamotrigine

The value of monitoring plasma concentrations of lamotrigine in patients treated with lamotrigine has not been established. Because of the possible pharmacokinetic interactions between lamotrigine and other drugs, including AEDs (see Table 13), 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.

The following serious adverse reactions are described in more detail in the Warnings and Precautions section of the labeling: Serious Skin Rashes [see Warnings and Precautions (5.1)]

Hemophagocytic Lymphohistiocytosis [see Warnings and Precautions (5.2)] Multiorgan Hypersensitivity Reactions and Organ Failure [see Warnings and Precautions (5.3)] Cardiac Rhythm and Conduction Abnormalities [see Warnings and Precautions (5.4)] Blood Dyscrasias [see Warnings and Precautions (5.5)] Suicidal Behavior and Ideation [see Warnings and Precautions (5.6)]

Aseptic Meningitis [see Warnings and Precautions (5.7)] Withdrawal Seizures [see Warnings and Precautions (5.10)] Status Epilepticus [see Warnings and Precautions (5.11)] Sudden Unexplained Death in Epilepsy [see Warnings and Precautions (5.12)]

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.

Most Common Adverse Reactions in All Clinical Trials: Adjunctive Therapy in Adults with Epilepsy: The most commonly observed (≥5% for lamotrigine and more common on drug than placebo) adverse reactions seen in association with lamotrigine during adjunctive therapy in adults and not seen at an equivalent frequency among placeho-treated natients were: dizziness, ataxia, somnolence, headache, diplonia blurred vision, nausea, vomiting, and rash. Dizziness, diplopia, ataxia, blurred vision, nausea, and vomiting were dose related. Dizziness, diplopia, ataxia, blurred vision, nausea, and vomiting were dose related. Dizziness, diplopia, ataxia, and blurred vision occurred more commonly in patients receiving carbamazepine with lamotrigine than in patients receiving other AEDs with lamotrigine. Clinical data suggest a higher incidence of rash, including serious rash, in patients receiving concomitan

alproate than in patients not receiving valproate [see Warnings and Precautions (5.1)]. Approximately 11% of the 3,378 adult patients who received lamotrigine as adjunctive therapy in premarketing clinical trials discontinued treatment because of an adverse reaction. The adverse reactions most commonly associated with discontinuation were rash (3.0%), dizziness (2.8%), and headache (2.5%).

In a dose-response trial in adults, the rate of discontinuation of lamotrigine for dizziness, ataxia, diplopia, blurred vision, nausea, and vomiting was dose related. Monotherapy in Adults with Epilepsy: The most commonly observed (≥5% for lamotrigine and more common on drug than placebo adverse reactions seen in association with the use of lamotrigine during the monotherapy phase of the controlled trial in adults not seen at an equivalent rate in the control group were vomiting, coordination abnormality, dyspepsia, nausea, dizziness, rhinitis, anxiety, insomnia,

infection, pain, weight decrease, chest pain, and dysmenorrhea. The most commonly observed (≥5% for lamotrigine and more common or drug than placebo) adverse reactions associated with the use of lamotrigine during the conversion to monotherapy (add-on) period, not seen at an equivalent frequency among low-dose valproate-treated patients, were dizziness, headache, nausea, asthenia, coordination abnormality, vomiting, rash, somnolence, diplopia, ataxia, accidental injury, tremor, blurred vision, insomnia, nystagmus, diarrhea, lymphadenopathy pruritus, and sinusitis. Approximately 10% of the 420 adult patients who received lamotrigine as monotherapy in premarketing clinical trials discontinued treatment

because of an adverse reaction. The adverse reactions most commonly associated with discontinuation were rash (4.5%), headache (3.1%), and asthenia (2.4%). drug than placebo) adverse reactions seen in association with the use of lamotrigine as adjunctive treatment in pediatric patients aged 2 to Adverse reactions seen in association with the use of lamotrigine as adjunctive treatment in pediatric patients aged 2 to Adverse reactions that occurred in at least 5% of patients and were numerically more frequent during the dose-escalation phase of the property of the p

In 339 patients aged 2 to 16 years with partial-onset seizures or generalized seizures of Lennox-Gastaut syndrome, 4.2% of patients on During the monotherapy phase of the double-blind, placebo-controlled trials of 18 months' duration, 13% of 227 patients who received lamotrigine and 2.9% of patients on placebo discontinued due to adverse reactions. The most commonly reported adverse reaction that led lamotrigine (100 to 400 mg/day), 16% of 190 patients who received placebo, and 23% of 166 patients who received lithium discontinued to discontinuation of lamotrigine was rash. Approximately 11.5% of the 1,081 pediatric patients aged 2 to 16 years who received lamotrigine as adjunctive therapy in premarketing

epilepsy treated with lamotrigine in placebo-controlled trials. In these trials, either lamotrigine or placebo was added to the patient's current among racial groups.

Body System/Adverse Reaction	Percent of Patients Receiving Adjunctive Lamotrigine (n = 711)	Percent of Patients Receiving Adjunctive Placebo (n = 419)	
Body as a whole			
Headache	29	19	
Flu syndrome	7	6	
Fever	6	4	
Abdominal pain	5	4	
Neck pain	2	1	
	2	1	
Reaction aggravated (seizure exacerbation)	2	1	
Digestive			
Nausea	19	10	
Vomiting	9	4	
Diarrhea	6	4	
Dyspepsia	5	2	
Constipation	4	3	
Anorexia	2	1	
Musculoskeletal			
Arthralgia	2	0	
Nervous			
Dizziness	38	13	
Ataxia	22	6	
Somnolence	14	7	
Incoordination	6	2	
Insomnia	6	2 2	
	_	1	
Tremor	4	1	
Depression	4	3	
Anxiety	4	3	
Convulsion	3	1	
Irritability	3	2	
Speech disorder	3	0	
Concentration disturbance	2	1	
Respiratory			
Rhinitis	14	9	
Pharyngitis	10	9	
Cough increased	8	6	
Skin and appendages			
Rash	10	5	
Pruritus	3	2	
Special senses			
Diplopia	28	7	
Blurred vision	16	5	
Vision abnormality	3	1	
Urogenital	<u> </u>	· · · · · ·	
Female patients only	(n = 365)	(n = 207)	
Dysmenorrhea	(II = 365) 7	(11 = 207)	
Vaginitis	4	1	
Amenorrhea	2 atients treated with lamotrigine and at a gre	1	

ratients in these adjunctive trials were receiving 1 to 3 of the concomitant antiepileptic drugs carbamazepine, phenytoin, phenobarbital, or primidone in addition to lamotrigine or placebo. Patients may have reported multiple adverse reactions during the trial or at discontinuation; thus, patients may be included in more than 1 category.

In a randomized, parallel trial comparing placebo with 300 and 500 mg/day of lamotrigine, some of the more common drug-related adverse reactions were dose related (see Table 9). Table 9. Dose-Related Adverse Reactions from a Randomized, Placebo-Controlled Adjunctive Trial in Adults with Epileps

	Percent of Patients Experiencing Adverse Reactions				
Adverse Reaction	Placebo (n = 73)	Lamotrigine 300 mg (n = 71)	Lamotrigine 500 mg (n = 72)		
taxia	10	10	28 ^{a, b}		
lurred vision	10	11	25 ^{a, b}		
iplopia	8	24 ^a	49 ^{a, b}		
izziness	27	31	54 ^{a, b}		
ausea	11	18	25 ^a		
omiting	4	11	18 ^a		
	(D 0 0F)				

non-Caucasian racial subgroup was only 6% of patients exposed to lamotrigine in placebo-controlled trials, there are insufficient data to support a statement regarding the distribution of adverse reaction reports by race. Generally, females receiving either lamotrigine as adjunctive therapy or placebo were more likely to report adverse reactions then make. The other disease of the property of the other disease of the property of the other disease of the property of the other disease of t The overall adverse reaction profile for lamotrigine was similar between females and males and was independent of age. Because the largest adjunctive therapy or placebo were more likely to report adverse reactions than males. The only adverse reaction for which the reports on Infrequent: Acne, alopecia, hirsutism, maculopapular rash, skin discoloration, urticaria. lamotrigine were > 10% more frequent in females than males (without a corresponding difference by gender on placebo) was dizziness

Controlled Monotherapy Trial in Adults with Partial-Onset Seizures: Table 10 lists adverse reactions that occurred in patients with Digestive System epilepsy treated with monotherapy with lamotrigine in a double-blind trial following discontinuation of either concomitant carbamazepine or Infrequent: Dysphagia, eructation, gastritis, gingivitis, increased aglivation, liver function tests abnormal, mouth

^b Significantly greater than group receiving lamotrigine 300 mg (*P*<0.05).

Body System/ Adverse Reaction	Percent of Patients Receiving Lamotrigine ^c as Monotherapy (n = 43)	Percent of Patients Receiving Low-Dose Valproate ^d Monothera (n = 44)	
Body as a whole			
Pain	5	0	
Infection	5	2	
Chest pain	5	2	
Digestive			
Vomiting	9	0	
Dyspepsia	7	2	
Nausea	7	2	
Metabolic and nutritional			
Weight decrease	5	2	
lervous			
Coordination abnormality	7	0	
Dizziness	7	0	
Anxiety	5	0	
Insomnia	5	2	
Respiratory			
Rhinitis	7	2	
Jrogenital (female patients only)	(n = 21)	(n = 28)	
Dysmenorrhea	5	0 '	

 $Adverse\ reactions\ that\ occurred\ in\ at\ least\ 5\%\ of\ patients\ treated\ with\ lamotrigine\ and\ at\ a\ greater\ incidence\ than\ valproate-treated\ patients.$ Patients in this trial were converted to lamotrigine or valproate monotherapy from adjunctive therapy with carbamazepine or phenytoin. Patients may have reported multiple adverse reactions during the trial; thus, patients may be included in more than 1 category c Up to 500 mg/day.

Adverse reactions that occurred with a frequency of <5% and >2% of patients receiving lamotrigine and numerically more frequent than Rare: Hiccup, hyperventilation. placebo were:

Body as a Whole: Asthenia, fever

Incidence in Controlled Adjunctive Trials in Pediatric Patients with Epilepsy: Table 11 lists adverse reactions that occurred in 339 pediatric patients with partial-onset seizures or generalized seizures of Lennox-Gastaut syndrome who received lamotrigine up to 15

Table 11. Adverse Reactions in Pooled, Placebo-Controlled Adjunctive Trials in Pediatric Patients with Epilepsy

Body System/ Adverse Reaction	Percent of Patients Receiving Lamotrigine (n = 168)	Percent of Patients Receiving Placebo (n = 171)		
Body as a whole	(1.111)	(11 11 1)		
Infection	20	17		
Fever	15	14		
Accidental injury	14	12		
Abdominal pain	10	5		
Asthenia	8	4		
Flu syndrome	7	6		
Pain	5	4		
Facial edema	2	1		
	2	0		
Photosensitivity	2	U		
Cardiovascular				
Hemorrhage	2	1		
Digestive				
Vomiting	20	16		
Diarrhea	11	9		
Nausea	10	2		
Constipation	4	2		
Dyspepsia	2	1		
Hemic and lymphatic		•		
Lymphadenopathy	2	1		
		'		
Metabolic and nutritional				
Edema	2	0		
Nervous system				
Somnolence	17	15		
Dizziness	14	4		
Ataxia	11	3		
Tremor	10	1		
Emotional lability	4	2		
Gait abnormality	4	2		
Thinking abnormality	3	2		
Convulsions	2	1		
Nervousness	2	1		
Vertigo	2	1		
	۷	I		
Respiratory				
Pharyngitis	14	11		
Bronchitis	7	5		
Increased cough	7	6		
Sinusitis	2	1		
Bronchospasm	2	1		
Skin				
Rash	14	12		
Eczema	2	1		
Pruritus	2	i		
Special senses				
Diplopia	5	1		
	4	1		
Blurred vision	2	1 0		
Visual abnormality	2	U		
Urogenital				
Male and female patients				
Urinary tract infection	3	0		

a Adverse reactions that occurred in at least 2% of patients treated with lamotrigine and at a greater incidence than placebo.

The most common adverse reactions seen in association with the use of lamotrigine as monotherapy (100 to 400 mg/day) in adult patients (aged 18 to 82 years) with bipolar disorder in the 2 double-blind, placebo-controlled trials of 18 months' duration are included in Table 12 16 years and not seen at an equivalent rate in the control group were infection, vomiting, rash, fever, somnolence, accidental injury, dizziness, diarrhea, abdominal pain, nausea, ataxia, tremor, asthenia, bronchitis, flu syndrome, and diplopia. lamotrigine in these trials (when patients may have been receiving concomitant medications) compared with the monotherapy phase were the deadche (25%), rash (11%), dizziness (10%), diarrhea (8%), dream abnormality (6%), and pruritus (6%).

therapy because of an adverse reaction. The adverse reactions that most commonly led to discontinuation of lamotrigine were rash (3%) and mania/hypomania/mixed mood adverse reactions (2%). Approximately 16% of 2,401 patients who received lamotrigine (50 to 500 m clinical trials discontinued treatment because of an adverse reaction. The adverse reaction most commonly associated with discontinuation were rash (4.4%), reaction aggravated (1.7%), and ataxia (0.6%).

Controlled Adjunctive Clinical Trials in Adults with Epilepsy: Table 8 lists adverse reactions that occurred in adult patients with engage of a patient of the patient's current and the patient's current a

Table 12. Adverse Reactions in 2 Placebo-Controlled Trials in Adult Patients with Bipolar I Disorde

Body System/ Adverse Reaction	Percent of Patients Receiving Lamotrigine (n = 227)	Percent of Patients Receiving Placebo (n = 190)	
General			
Back pain	8	6	
Fatigue	8	5	
Abdominal pain	6	3	
Digestive			
Nausea	14	11	
Constipation	5	2	
Vomiting	5	2	
Nervous System			
Insomnia	10	6	
Somnolence	9	7	
Xerostomia (dry mouth)	6	4	
Respiratory			
Rhinitis	7	4	
Exacerbation of cough	5	3	
Pharyngitis	5	4	
Skin			
Rash (nonserious) ^c	7	5	
Patients in these trials were converted to la	ast 5% of patients treated with lamotrigine amotrigine (100 to 400 mg/day) or placebo me reported multiple adverse reactions during the rs clinical trials, the rate of serious rash was 0.00	onotherapy from add-on therapy	

Other reactions that occurred in 5% or more patients but equally or more frequently in the placebo group included: dizziness, mania, headache, infection, influenza, pain, accidental injury, diarrhea, and dyspepsia Adverse reactions that occurred with a frequency of <5% and >1% of patients receiving lamotrigine and numerically more frequent than

General: Fever, neck pain. Cardiovascular: Migraine. Digestive: Flatulence. Metabolic and Nutritional: Weight gain, edema

Musculoskeletal: Arthralgia, myalgia Nervous System: Amnesia, depression, agitation, emotional lability, dyspraxia, abnormal thoughts, dream abnormality, hypoesthesia. Respiratory: Sinusitis. Urogenital: Urinary frequency

Adverse Reactions following Abrupt Discontinuation: In the 2 controlled clinical trials, there was no increase in the incidence, severity, or type of adverse reactions in patients with bipolar disorder after abruptly terminating therapy with lamotrigine. In the clinical development program in adults with bipolar disorder, 2 patients experienced seizures shortly after abrupt withdrawal of lamotrigine [see Warnings and Precautions

Mania/Hypomania/Mixed Episodes: During the double-blind, placebo-controlled clinical trials in bipolar I disorder in which adults were converted to monotherapy with lamotrigine (100 to 400 mg/day) from other psychotropic medications and followed for up to 18 months, the rates of manic or hypomanic or mixed mood episodes reported as adverse reactions were 5% for patients treated with lamotrigine (n = 227), 4% for patients treated with lithium (n = 166), and 7% for patients treated with placebo (n = 190). In all bipolar controlled trials combined, adverse reactions of mania (including hypomania and mixed mood episodes) were reported in 5% of patients treated with lamotrigine (n = 956), 3% of patients treated with lithium (n = 280), and 4% of patients treated with placebo (n = 803). 6.2 Other Adverse Reactions Observed in All Clinical Trials

Lamotrigine has been administered to 6,694 individuals for whom complete adverse reaction data was captured during all clinical trials, only some of which were placebo controlled. During these trials, all adverse reactions were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse reactions, similar types of adverse reactions were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. The frequencies presented represent the proportion of the 6,694 individuals exposed to lamotrigine who experienced an event of the type cited on at least 1 occasion while receiving lamotrigine. All reported adverse reactions are included except those already listed in the previous tables or elsewhere in the labeling, those too general to be informative, and those not reasonably associated with the use of the drug. Adverse reactions are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse reactions are defined as those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1,000 patients; rare adverse reactions are those occurring in fewer than 1/1,000 patients.

Body as a Whole Infrequent: Allergic reaction, chills, malaise Cardiovascular System

(difference = 16.5%). There was little difference between females and males in the rates of discontinuation of lamotrigine for individual and the control of lam pustular rash, Stevens-Johnson syndrome, vesiculobullous rash.

Rare: Gastrointestinal hemorrhage, glossitis, gum hemorrhage, gum hyperplasia, hematemesis, hemorrhagic colitis, hepatitis, melena, stomach ulcer, stomatitis, tongue edema. Endocrine System Rare: Goiter, hypothyroidis Hematologic and Lymphatic System

Rare: Anemia, eosinophilia, fibrin decrease, fibrinogen decrease, iron deficiency anemia, leukocytosis, lymphocytosis, macrocytic anemia petechia, thrombocytopenia. Metabolic and Nutritional Disorders Infrequent: Aspartate transaminase increased. Rare: Alcohol intolerance, alkaline phosphatase increase, alanine transaminase increase, bilirubinemia, general edema, gamma glutamyl

Musculoskeletal System Infrequent: Arthritis, leg cramps, myasthenia, twitching.

Rare: Bursitis, muscle atrophy, pathological fracture, tendinous contracture.

Nervous System

Infrequent: Akathisia, apathy, aphasia, central nervous system 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, sleep disorder, stupor, suicidal ideation

Respiratory System

Infrequent: Ecchymosis, leukopenia

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, peripheral

Infrequent: Yawn. Special Senses

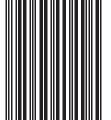
Frequent: Amblyopia. Infrequent: Abnormality of accommodation, conjunctivitis, dry eyes, ear pain, photophobia, taste perversion, tinnitus, Rare: Deafness, lacrimation disorder, oscillopsia, parosmia, ptosis, strabismus, taste loss, uveitis, visual field defect.

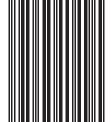
Infrequent: Abnormal ejaculation, hematuria, impotence, menorrhagia, polyuria, urinary incontinence.



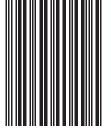


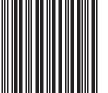






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Rare: Acute kidney failure, anorgasmia, breast abscess, breast neoplasm, creatinine increase, cystitis, dysuria, epididymitis, female lactation, 11 DESCRIPTION kidney failure, kidney pain, nocturia, urinary retention, urinary urgency. 6.3 Postmarketing Experience

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

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

Gastrointestinal Esophagitis.

Hepatobiliary Tract and Pancreas

Pancreatitis.

<u>Immunologic</u> Hypogammaglobulinemia, lupus-like reaction, vasculitis

Lower Respiratory

<u>Musculoskeletal</u> Rhabdomyolysis has been observed in patients experiencing hypersensitivity reactions.

Nervous System Aggression, exacerbation of Parkinsonian symptoms in patients with pre-existing Parkinson's disease, tics. Non-site Specific

Progressive immunosuppression

Renal and Urinary Disorders Fubulointerstitial nephritis (has been reported alone and in association with uveitis).

DRUG INTERACTIONS Significant drug interactions with lamotrigine are summarized in this section.

Uridine 5´-diphospho-glucuronyl transferases (UGT) have been identified as the enzymes responsible for metabolism of lamotrigine. Drugs that induce or inhibit glucuronidation may, therefore, affect the apparent clearance of lamotrigine. Strong or moderate inducers of the cytochrome P450 3A4 (CYP3A4) enzyme, which are also known to induce UGT, may also enhance the metabolism of lamotrigine. Those drugs that have been demonstrated to have a clinically significant impact on lamotrigine metabolism are outlined in Table 13. Specific dosing guidance for these drugs is provided in the Dosage and Administration section [see Dosage and Administration (2.1)].

Additional details of these drug interaction studies are provided in the Clinical Pharmacology section [see Clinical Pharmacology (12.3)]. Table 13. Established and Other Potentially Significant Drug Interactions

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

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

Effect of Lamotrigine on Organic Cationic Transporter 2 Substrates

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

USE IN SPECIFIC POPULATIONS Pregnancy

Risk Summary

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

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

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

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

Human Data: Data from several international pregnancy registries have not shown an increased risk for malformations overall. The

International Lamotrigine Pregnancy Registry reported major congenital malformations in 2.2% (95% CI: 1.6%, 3.1%) of 1,558 infants exposed to lamotrigine monotherapy in the first trimester of pregnancy. The NAAED Pregnancy Registry reported major congenital malformations among 2.0% of 1,565 infants exposed to lamotrigine monotherapy in the first trimester EURAP, a large international pregnancy registry focused outside of North America, reported major birth defects in 2.9% (95% CI: 2.3%, 3.7%) of 2,514 exposures to amotriging monotherapy in the first trimester. The frequency of major congenital malformations was similar to estimates from the general

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

Several meta-analyses have not reported an increased risk of major congenital malformation types were observed.

Lamotrigine is rapidly and completely absorbed after oral administration with negligible first-pass metabolism (absolute bioavailability is compared with healthy and disease-matched controls. No patterns of specific malformation types were observed.

Lamotrigine is rapidly and completely absorbed after oral administration with negligible first-pass metabolism (absolute bioavailability is soft affected by food. Peak plasma concentrations occur anywhere from 1.4 to 4.8 hours following drug deministration. The same meta-analyses evaluated the risk of additional maternal and infant outcomes including fetal death, stillbirth, preterm birth, small for gestational age, and neurodevelopmental delay. Although there are no data suggesting an increased risk of these outcomes with

In healthy volunteers not receiving any other medications and given single doses, the plasma concentrations of lamotrigine increased in healthy volunteers not receiving any other medications and given single doses, the plasma concentrations of lamotrigine increased in healthy volunteers not receiving any other medications and given single doses, the plasma concentrations of lamotrigine increased in direct proportion to the dose administered over the range of 50 to 400 mg. In 2 small studies (n = 7 and 8) of patients with epilepsy who were maintained on other AEDs, there also was a linear relationship between dose and lamotrigine plasma concentrations at steady state following that can be drawn. Animal Data: When lamotrigine was administered to pregnant mice, rats, or rabbits during the period of organogenesis (oral doses of up to doses of 50 to 350 mg twice daily. 125, 25, and 30 mg/kg, respectively), reduced fetal body weight and increased incidences of fetal skeletal variations were seen in mice and rats at doses that were also maternally toxic. The no-effect doses for embryofetal developmental toxicity in mice, rats, and rabbits (75, 6.25,

and 30 mg/kg, respectively) are similar to (mice and rabbits) or less than (rats) the human dose of 400 mg/day on a body surface area (mg/m²) basis.

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.

When administered to pregnant rats, lamotrigine decreased fetal folate concentrations at doses greater than or equal to 5 mg/kg/day, which is less than the human dose of 400 mg/day on a mg/m² basis.

Lactation

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 ¹⁴C-lamotrigine (15 µCi) to 6 healthly volunteers, 94% was recovered in the urine and 2% was recovered in the fees. The radioactivity in the urine consisted of on unchanged landow of unchanged landow of unchanged landow in the fees. The radioactivity in the urine consisted of on unchanged landow in the fees. The radioactivity in the urine consisted of on unchanged landow in the fees. The radioactivity in the urine consisted of on unchanged landow in the fees. The radioactivity in the urine consisted of unchanged landow in the fees. The radioactivity in the urine consisted of unchanged landow in the fees. The radioactivity in the urine consisted of unchanged landow in the fees. The radioactivity in the urine consisted of unchanged landow.

Risk Summary
Lamotrigine is present in milk from lactating women taking lamotrigine tablets (see Data). Neonates and young infants are at risk for high Enzyme Induction
The effects of lamotrigine is present in milk from lactating women taking lamotrigine tablets (see Data). Neonates and young infants are at risk for high The effects of lamotrigine is present in milk from lactating women taking lamotrigine tablets (see Data). Neonates and young infants are at risk for high The effects of lamotrigine is present in milk from lactating women taking lamotrigine tablets (see Data). Neonates and young infants are at risk for high The effects of lamotrigine is present in milk from lactating women taking lamotrigine tablets (see Data). Neonates and young infants are at risk for high The effects of lamotrigine tablets (see Data). Lamotrigine is present in milk from lactating women taking lamotrigine tablets (*see Data*). Neonates and young infants are at risk for high serum levels because maternal serum and milk levels can rise to high levels postpartum if lamotrigine dosage has been increased during pregnancy but is not reduced after delivery to the pre-pregnancy dosage. Glucuronidation is required for drug clearance. Glucuronidation capacity is immature in the infant and this may also contribute to the level of lamotrigine exposure. Events including rash, apnea, drowsiness, poor sucking, and poor weight gain (requiring hospitalization in some cases) have been perported in infants who have been human milk-fed with the present of the present he drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for lamotrigine and any glucuronidation [see Drug Interactions (7)].

luman milk-fed infants should be closely monitored for adverse events resulting from lamotrigine. Measurement of infant serum levels

8.4 Pediatric Use

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

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

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

n a juvenile animal study in which lamotrigine (oral doses of 0, 5, 15, or 30 mg/kg) was administered to young rats from postnatal day 7 to 62, decreased viability and growth were seen at the highest dose tested and long-term neurobehavioral abnormalities (decreased locomotor activity, increased reactivity, and learning deficits in animals tested as adults) were observed at the 2 highest doses. The no-effect dose for adverse developmental effects in juvenile animals is less than the human dose of 400 mg/day on a mg/m² basis

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

8.6 Hepatic Impairment Experience in patients with hepatic impairment is limited. Based on a clinical pharmacology study in 24 subjects with mild, moderate, and experience in patients with negation inpairment is limited. Based on a clinical pharmacology study in 124 Subjects with mild, moderate, and severe liver impairment [see Clinical Pharmacology (12.3)], the following general recommendations can be made. No dosage adjustment is needed in patients with mild liver impairment. Initial, escalation, and maintenance doses should generally be reduced by approximately 25% in patients with moderate and severe liver impairment without ascites and 50% in patients with severe liver impairment with ascites.

Escalation and maintenance doses may be adjusted according to clinical response [see Dosage and Administration (2.1)].

8.7 Renal Impairment Lamotrigine is metabolized mainly by glucuronic acid conjugation, with the majority of the metabolites being recovered in the urine. In a small nparing a single dose of lamotrigine in subjects with varying degrees of renal impairment with healthy volunteers, the plasma lamotrigine was approximately twice as long in the subjects with chronic renal failure [see Clinical Pharmacology (12.3)]. Initial doses of lamotrigine should be based on patients' AED regimens; reduced maintenance doses may be effective for patients with significant renal impairment. Few patients with severe renal impairment have been evaluated during chronic treatment with lamotrigine.

*Not administered, but an active metabolite of oxcarbazepine.**

*Not administered, but an active metabolite of oxcarbazepine.**

10 OVERDOSAGE

10.1 Human Overdose Experience

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

10.2 Management of Overdose There are no specific antidotes for lamotrigine. Following a suspected overdose, hospitalization of the patient is advised. General supportive care is indicated, including frequent monitoring of vital signs and close observation of the patient. If indicated, emesis should be induced; usual precautions should be taken to protect the airway. It should be kept in mind that immediate-release lamotrigine is rapidly absorbed [see of the inactive normone preparation compared with trough lamotrigine concentrations at the end of the active normone cycle.

Of the inactive normone preparation compared with trough lamotrigine concentrations at the end of the active normone cycle.

Gradual transient increases in lamotrigine plasma levels (approximate 2-fold increase) occurred during the week of inactive normone preparation. Clinical Pharmacology (12.3)]. It is uncertain whether hemodialysis is an effective means of removing lamotrigine from the blood. In 6 renal Control Training Didgy (12.5); Its substrain whether lemonarys is a relective means of removing landing and remove and a failure patients, about 20% of the amount of lamotrigine in the body was removed by hemodialysis during a 4-hour session. A Poison Control Center should be contacted for information on the management of overdosage of lamotrigine.

Lamotrigine, USP an AED of the phenyltriazine class, is chemically unrelated to existing AEDs. Lamotrigine's chemical name is 3,5-diamino-6-(2,3-dichlorophenyl)-as-triazine, its molecular formula is C₂H,N,Cl₃, and its molecular weight is 256.09. Lamotrigine, USP is a white to pale cream-colored powder and has a pK, of 5.7. Lamotrigine, USP is very slightly soluble in water (0.17 mg/mL at 25°C) and slightly soluble in 0.1 M HCl (4.1 mg/mL at 25°C). The structural formula is:

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

Meets USP Dissolution Test 3 CLINICAL PHARMACOLOGY

ne precise mechanism(s) by which lamotrigine exerts its anticonvulsant action are unknown. In animal models designed to detect inticonvulsant 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. he 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 nembranes and consequently modulating presynaptic transmitter release of excitatory amino acids (e.g., glutamate and aspartate).

Atazanavir/Ritonavir In a study in healthy with the study in healthy with the

Effect of Lamotrigine on N-Methyl d-Aspartate-Receptor-Mediated Activity Lamotrigine did not inhibit N-methyl d-aspartate (MMDA)-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 (CNDX, CGS, TCHP). The IC₉₉ for lamotrigine effects on NMDA-induced currents (in the presence of 3 µM of glycine) in cultured hippocampal neurons exceeded 100 µM.

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

12.2 Pharmacodynamics Folate Metabolism

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

Effect of Lamotrigine Metabolite: In dogs, lamotrigine is extensively metabolized to a 2-N- methyl metabolite. This metabolite causes dose-dependent prolongation of the PR interval, widening of the QRS complex, and, at higher doses, complete AV conduction block. The in vitro electrophysiological effects of this metabolite have not been studied. Similar cardiovascular effects from this metabolite are not anticipated in humans because only trace amounts of the 2-N-methyl metabolite could be increased in patients with a reduced capacity to glucuronidate lamotrigine (e.g., in patients with liver disease, patients taking concomitant medications that inhibit later than the conduction story of the properties of

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

Lamotrigine binds to melanin-containing tissues, e.g., in the eye and pigmented skin. It has been found in the uveal tract up to 52 weeks after a single dose in rodents. 12.3 Pharmacokinetics

The pharmacokinetics of lamotrigine have been studied in subjects with epilepsy, healthy young and elderly volunteers, and volunteers with chronic renal failure. Lamotrigine pharmacokinetic parameters for adult and pediatric subjects and healthy normal volunteers are summarized in Tables 14 and 16. Table 14. Mean Pharmacokinetic Parameters^a in Healthy Volunteers and Adult Subjects with Epilepsy

Adult Study Population	Number of Subjects	T _{max} : Time of Maximum Plasma Concentration (h)	t _{1/2} : Elimination Half-life (h)	CL/F: Apparent Plasma Clearance (mL/min/kg)
Healthy volunteers taking no	,	. ,	,	(1 1 0)
other medications:				
Single-dose Lamotrigine	179	2.2	32.8	0.44
		(0.25 to 12.0)	(14.0 to 103.0)	(0.12 to 1.10)
Multiple-dose Lamotrigine	36	1.7	25.4	0.58
		(0.5 to 4.0)	(11.6 to 61.6)	(0.24 to 1.15)
Healthy volunteers taking valproate:				
Single-dose Lamotrigine	6	1.8 (1.0 to 4.0)	48.3 (31.5 to 88.6)	0.30 (0.14 to 0.42)
Multiple-dose Lamotrigine	18	1.9	70.3	0.18
		(0.5 to 3.5)	(41.9 to 113.5)	(0.12 to 0.33)
Subjects with epilepsy taking valproate only:				
Single-dose Lamotrigine	4	4.8	58.8	0.28
		(1.8 to 8.4)	(30.5 to 88.8)	(0.16 to 0.40)
Subjects with epilepsy taking carbamazepine, phenytoin, phenobarbital, or primidone ^b plus valproate:				
Single-dose Lamotrigine	25	3.8	27.2	0.53
		(1.0 to 10.0)	(11.2 to 51.6)	(0.27 to 1.04)
Subjects with epilepsy taking carbamazepine, phenytoin,				
phenobarbital, or primidone ^b :			l	
Single-dose Lamotrigine	24	2.3	14.4	1.10
Multiple-dose Lamotrigine	17	(0.5 to 5.0) 2.0	(6.4 to 30.4) 12.6	(0.51 to 2.22) 1.21
Multiple-dose Lamotrigine	17	(0.75 to 5.93)	(7.5 to 23.1)	(0.66 to 1.82)
	1	(0.75 to 5.55)	(1.0 (0 20.1)	(0.00 (0 1.02)

The majority of parameter means determined in each study had coefficients of variation between 20% and 40% for half-life and CL/F and Topiramate resulted in no change in plasma concentrations of lamotrigine. Administration of lamotrigine resulted in a 15% increase in between 30% and 70% for T_{max}. The overall mean values were calculated from individual study means that were weighted based on the number of volunteers/subjects in each study. The numbers in parentheses below each parameter mean represent the range of individual volunteer/subject values across studies.

taining oral contraceptives and other drugs, such as rifampin and protease in that induce lamotrigine glucuronidation have also been shown to increase the apparent clearance of lamotrigine [see Drug Interactions (7)]. Absorption

at the higher dose tested.

When pregnant rats were administered lamotrigine (oral doses of 0, 5, 10, or 20 mg/kg) during the latter part of gestation and throughout lactation, increased offspring mortality (including stillbirths) was seen at all doses. The lowest effect dose for pre- and post-natal doses tested.

When administered to a recomplete the controlled to a recomplete to the controlled efficacy trials). The binding of lamotrigine is approximately 55% bound to human plasma proteins at plasma lamotrigine is unlikely to be reduced by concomitant administration of amitript concentrations specified to the controlled efficacy trials). The 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). The concentration observed in the controlled efficacy trials). The concentration observed in the controlled efficacy trials). The concentration observed in the controlled efficacy trials. The co

a 2-N-methyl metabolite (0.14%), and other unidentified minor metabolites (4%).

pregnancy but is not reduced after delivery to the pre-pregnancy dosage. Glucuronidation is required for drug clearance. Glucuronidation appearance, but is not reduced after delivery to the pre-pregnancy dosage. Glucuronidation is required for drug clearance. Glucuronidation may be appearance on the properties of the

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

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

Drug Interactions (7.1)

Pure Interactions (7.1) The net effects of drug interactions with lamotrigine are summarized in Tables 13 and 15, followed by details of the drug interaction studies

Drug	Drug Plasma Concentration with Adjunctive Lamotrigine ^a	Lamotrigine Plasma Concentration with Adjunctive Drugs ^b	
Oral contraceptives (e.g., ethinylestradiol/levonorgestrel) ^c	⇔ ^d	↓ ↓	
Aripiprazole	Not assessed	<> ⁶	
Atazanavir/ritonavir	⇔f	↓	
Bupropion	Not assessed	↔	
Carbamazepine	↔	1	
Carbamazepine epoxideg	?		
Felbamate	Not assessed	↔	
Gabapentin	Not assessed	↔	
Lacosamide	Not assessed	↔	
Levetiracetam	↔	↔	
Lithium	↔	Not assessed	
Lopinavir/ritonavir	⇔⁰	↓	
Olanzapine	↔	€>6	
Oxcarbazepine	↔	↔	
10-Monohydroxy oxcarbazepine metabolite ^h	↔		
Perampanel	Not assessed	<> ⁶	
Phenobarbital/primidone	↔	↓	
Phenytoin	↔	↓	
Pregabalin	↔	↔	
Rifampin	Not assessed	↓	
Risperidone	↔	Not assessed	
9-Hydroxyrisperidone ⁱ	↔		
Topiramate	⇔j	↔	
Valproate	↓	↑	
Valproate + phenytoin and/or			
carbamazepine	Not assessed	↔	
Zanisamida	Nat assess	1	

Net effects were estimated by comparing the mean clearance values obtained in adjunctive clinical trials and volunteer trials. 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/

d Modest decrease in levonorgestre e Slight decrease, not expected to be clinically meaningful.

Table 15. Summary of Drug Interactions with Lamotrigine

Because there is inadequate experience in this population, lamotrigine should be used with caution in these patients [see Dosage and Not administered, but an active metabolite of risperidone Slight increase, not expected to be clinically meaningful.

> of the inactive hormone preparation compared with trough lamotrigine concentrations at the end of the active hormone cycle. (pill-free week) for women not also taking a drug that increased the clearance of lamotrigine (carbamazepine, phenytoin, phenobarbital, pheno the few days before or during the pill-free week. Increases in lamotrigine plasma levels could result in dose-dependent adverse reactions.

In the same study, coadministration of lamotrigine (300 mg/day) in 16 female volunteers did not affect the pharmacokinetics of the ethinylestradiol component of the oral contraceptive preparation. There were mean decreases in the AUC and C_{max} of the levonorgestrel component of 19% and 12%, respectively. Measurement of serum progesterone indicated that there was no hormonal evidence of ovulation in any of the 16 volunteers, although measurement of serum FSH, LH, and estradiol indicated that there was some loss of suppression of the brondhalamic-nituitary-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 Trial endpoints were completion of all weeks of trial treatment or meeting an escape criterion. Criteria for escape relative to baseline were: (1) 17 PATIENT COUNSELING INFORMATION ontraceptive efficacy in some patients cannot be excluded. Therefore, patients should be instructed to promptly report changes in their nenstrual pattern (e.g., break-through bleeding).

Dosage adjustments may be necessary for women receiving estrogen-containing oral contraceptive preparations [see Dosage and Administration (2.11)]. Other Hormonal Contraceptives or Hormone Replacement Therapy

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

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 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 Ilse in Specific Populations (8.11) Enlarge concentrations. Lamotrigine has no appreciable effect on steady-state carbamazepine plasma concentration. Limited clinical data suggest there is a higher rais during organogenesis, tetal, 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.

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.

The pharmacokinetics of lithium were not altered in healthy subjects (n = 20) by coadministration of lamotrigine (100 mg/day) for 6 days. Lopinavir/Ritonavir The addition of lopinavir (400 mg twice daily)/ritonavir (100 mg twice daily) decreased the AUC, C_{max}, and elimination half-life of lamotrigine by approximately 50% to 55.4% in 18 healthy subjects. The pharmacokinetics of lopinavir/ritonavir were similar with concomitant lamotrigine, compared with that in historical controls.

Olanzapine The AUC and C_{max} of olanzapine were similar following the addition of olanzapine (15 mg once daily) to lamotrigine (200 mg once daily) in healthy male volunteers (n = 16) compared with the AUC and C_{max} in healthy male volunteers receiving olanzapine alone (n = 16). In the same trial, the AUC and C_{max} of lamotrigine were reduced on average by 24% and 20%, respectively, following the addition of olanzapine to lamotrigine in healthy male volunteers compared with those receiving lamotrigine alone. This reduction in lamotrigine plasma concentrations is not expected to be clinically meaningful.

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). make volunteers receiving oxcaroazepine alone (n = 13).

The primary efficacy endpoint was percentage change from baseline in PGTC seizures. For the intent-to-treat population, the median percent healthy male volunteers compared with change of headache, distributes and some places and compared with cardinistration of lamotrigine alone. Limited clinical data suggest a higher incidence of headache, distributes and compared with lamotrigine and expenditure of lam dizziness, nausea, and somnolence with coadministration of lamotrigine and oxcarbazepine compared with lamotrigine alone or

In a pooled analysis of data from 3 placebo-controlled clinical trials investigating adjunctive perampanel in patients with partial-onset and The effectiveness of lamotrigine in the maintenance treatment of bipolar I disorder was established in 2 multicenter, double-blind effect of this magnitude is not considered to be clinically relevant.

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

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

In 10 male volunteers, rifampin (600 mg/day for 5 days) significantly increased the apparent clearance of a single 25-mg dose of lamotrigine

In a 14 healthy volunteers study, multiple oral doses of lamotrigine 400 mg daily had no clinically significant effect on the single-dose in Trial 2, patients received double-blind monotherapy with lamotrigine (100 to 400 mg/day, n = 59), or placebo (n = 70). Lamotrigine was a function of repartitions and the single-dose in Trial 2, patients received double-blind monotherapy with lamotrigine (100 to 400 mg/day, n = 59), or placebo (n = 70). Lamotrigine was a function of the single-dose in Trial 2, patients received double-blind monotherapy with lamotrigine (100 to 400 mg/day, n = 59), or placebo (n = 70). Lamotrigine was a function of the single-dose in Trial 2, patients received double-blind monotherapy with lamotrigine (100 to 400 mg/day, n = 59), or placebo (n = 70). Lamotrigine was a function of the single-dose in Trial 2, patients received double-blind monotherapy with lamotrigine (100 to 400 mg/day, n = 59), or placebo (n = 70). Lamotrigine was a function of the single-dose in Trial 2, patients received double-blind monotherapy with lamotrigine (100 to 400 mg/day, n = 59), or placebo (n = 70). Lamotrigine was a function of the single-dose in Trial 2, patients received double-blind monotherapy with lamotrigine (100 to 400 mg/day, n = 59), or placebo (n = 70). Lamotrigine was a function of the single-dose in Trial 2, patients received double-blind monotherapy with lamotrigine (100 to 400 mg/day). pharmacokinetics of risperidone 2 mg and its active metabolite 9-OH risperidone. Following the coadministration of risperidone 2 mg with lamotrigine, 12 of the 14 volunteers reported somnolence compared with 1 out of 20 when risperidone was given alone, and none when

topiramate concentrations 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. Carbamazepine, phenytoin, phenobarbital, and primidone have been shown to increase the apparent clearance of lamotrigine.

The addition of valproate increased lamotrigine steady-state concentrations in normal volunteers by slightly more than 2-fold. In 1 trial, maximal inhibition of lamotrigine clearance was reached at valproate doses between 250 and 500 mg/day and did not increase as the In a study in 18 patients with epilepsy, coadministration of zonisamide (200 to 400 mg/day) with lamotrigine (150 to 500 mg/day for 35 days)

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

In vitro assessment of the inhibitory effect of lamotrigine at OCT2 demonstrate that lamotrigine, but not the N(2)-glucuronide metabolite, is an inhibitor of OCT2 at potentially clinically relevant concentrations, with IC_{50} value of 53.8 μ M [see Drug Interactions (7)]. Results of in vitro experiments suggest that clearance of lamotrigine is unlikely to be reduced by concomitant administration of amitriptyline, clonazepam, clozapine, fluoxetine, haloperidol, lorazepam, phenelzine, sertraline, or trazodone.

Patients with Renal Impairment: Twelve volunteers with chronic renal failure (mean creatinine clearance: 13 mL/min, range: 6 to 23) and another 6 individuals undergoing hemodialysis were each given a single 100-mg dose of lamotrigine. The mean plasma half-lives determined in the study were 42.9 hours (chronic renal failure), 13.0 hours (during hemodialysis), and 57.4 hours (between hemodialysis) compared with 26.2 hours in healthy volunteers. On average, approximately 20% (range: 5.6 to 35.1) of the amount of lamotrigine present in the body was eliminated by hemodialysis during a 4-hour session [see Dosage and Administration (2.1)]. Patients with Hepatic Impairment: The pharmacokinetics of lamotrigine following a single 100-mg dose of lamotrigine were evaluated in 24 subjects with mild, moderate, and severe hepatic impairment (Child-Pugh classification system) and compared with 12 subjects without nepatic impairment. The subjects with severe hepatic impairment were without ascites (n = 2) or with ascites (n = 5). The mean apparent clearances of lamotrigine in subjects with mild (n = 12), moderate (n = 5), severe without ascites (n = 2), and severe with ascites (n = 5) liver impairment were 0.30 ± 0.09, 0.24 ± 0.1, 0.21 ± 0.04, and 0.15 ± 0.09 mL/min/kg, respectively, as compared with 0.37 ± 0.1 mL/min/kg in the healthy controls. Mean half-lives of lamotrigine in subjects with mild, moderate, severe without ascites, and severe with ascites hepatic impairment were 46 ± 20, 72 ± 44, 67 ± 11, and 100 ± 48 hours, respectively, as compared with 33 ± 7 hours in healthy controls [see Dosage and Administration (2.1)].

primidone, or other drugs such as rifampin and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir that induce lamotrigine Pediatric Patients: The pharmacokinetics of lamotrigine following a single 2-mg/kg dose were evaluated in 2 studies in pediatric subjects (n = 29 for subjects aged 10 months to 5.9 years and n = 26 for subjects aged 5 to 11 years). Forty-three subjects received cond with other AEDs and 12 subjects received lamotrigine as monotherapy. Lamotrigine pharmacokinetic parameters for pediatric patients are summarized in Table 16.

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

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

Carbamazepine, phenytoin, phenobarbital, and primidone have been shown to increase the apparent clearance of lamotrigine. Estrogen-containing oral contraceptives, rifampin, and the protease inhibitors lopinavir/ritonavir and atazanavir/ritonavir have also been shown to increase the apparent clearance of lamotrigine [see Drug Interactions (7)]. Two subjects were included in the calculation for mean T_{max}

Geriatric Patients: The pharmacokinetics of lamotrigine following a single 150-mg dose of lamotrigine were evaluated in 12 elderly volunteers between the ages of 65 and 76 years (mean creatinine clearance = 61 mL/min, range: 33 to 108 mL/min). The mean half-life of lamotrigine 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 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 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 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 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 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 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). in these subjects was 31.2 hours (range: 24.5 to 43.4 hours), and the mean clearance was 0.40 mL/min/kg (range: 0.26 to 0.48 mL/min/kg) Male and Female Patients: The clearance of lamotrigine is not affected by gender. However, during dose escalation of lamotrigine in 1 clinical trial in patients with epilepsy on a stable dose of valproate (n = 77), mean trough lamotrigine concentrations unadjusted for weight were 24% to 45% higher (0.3 to 1.7 mcg/mL) in females than in males.

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

NONCLINICAL TOXICOLOGY

clearance in adults were found to have similar effects in children.

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 of 39%. In this and in vivo rat bone marrow) assays.

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

Blister pack of 42, 25-mg tablets and 7, 100-mg tablets and 7, 100-mg tablets and 7, 100-mg tablets.

Study, trough serum lamotrigine concentrations gradually increased and were approximately 2-fold with mean decreases in AUC of 52% and in C of 39%. In this and in vivo rat bone marrow) assays.

No evidence of impaired fertility was detected in rats given oral doses of lamotrigine up to 20 mg/kg/day. The highest dose tested is less than the result of the control of the c

the human dose of 400 mg/day on a mg/m² basis. 14 CLINICAL STUDIES (pill-free Week) for women not also daming a unique that increased the obstance of lamotragine periodicine, or other drugs such as riflampin and the protease inhibitors (opinionavir/rithanivir and atazanavir/rithonavir that induce lamotrigine and atazanavir/rithonavir that induce lamotrigine purpose such as riflampin and the protease inhibitors (opinionavir/rithanivir and atazanavir/rithonavir that induce lamotrigine purpose such as riflampin and the protease inhibitors (opinionavir/rithanivir and atazanavir/rithonavir that induce lamotrigine purpose such as riflampin and the protease inhibitors (opinionavir/rithanivir and atazanavir/rithonavir that induce lamotrigine purpose such as riflampin and the protease inhibitors (opinionavir/rithanivir and atazanavir/rithonavir that induce lamotrigine purpose such as riflampin and the protease inhibitors (opinionavir/rithanivir and atazanavir/rithonavir that induce lamotrigine purpose such as riflampin and the protease inhibitors (opinionavir/rithonavir that induce lamotrigine purpose such as riflampin and the protease inhibitors (opinionavir/rithonavir that induce lamotrigine purpose such as riflampin and the protease inhibitors (opinionavir/rithonavir that induce lamotrigine purpose such as riflampin and atazanavir/rithonavir that induce lamotrigine purpose such as riflampin and atazanavir/rithonavir that induce lamotrigine purpose such as riflampin and atazanavir/rithonavir that induce lamotrigine purpose such as riflampin and atazanavir/rithonavir that induce lamotrigine purpose such as riflampin and atazanavir/rithonavir that induce lamotrigine purpose such as riflampin and atazanavir/rithonavir that induce lamotrigine purpose such as riflampin and atazanavir/rithonavir that induce lamotrigine purpose such as riflampin and atazanavir/rithonavir that induce lamotrigine purpose such as riflampin and atazanavir/rithonavir that induce lamotrigine purpose such as riflampin and atazanavir/rithonavir that induce lamotrigine purpose such as riflampin and atazanavir/rithon Phenobarbital, or Primidone as the Single Antiepileptic Drug

period. Patients were then converted to monotherapy with lamotrigine or valproate during the next 4 weeks, then continued on monotherapy

Storage for an additional 12-week period.

doubling of average monthly seizure count, (2) doubling of highest consecutive 2-day seizure frequency, (3) emergence of a new seizure type (defined as a seizure that did not occur during the 8-week baseline) that is more severe than seizure types that occur during study treatment, or (4) clinically significant prolongation of generalized tonic-clonic seizures. The primary efficacy variable was the proportion of patients in each treatment group who met escape criteria.

The percentages of patients who met escape criteria were 42% (32/76) in the group receiving lamotrigine and 69% (55/80) in the valproate group. The difference in the percentage of patients meeting escape criteria was statistically significant (P = 0.0012) in favor of lamotrigine. lymphadenopathy) may herald a serious medical event and instruct them to report any such occurrence to their healthcare providers Hemophagocytic Lymphohistiocytosis No differences in efficacy based on age, sex, or race were detected. Prior to initiation of treatment with lamotrigine, inform patients that excessive immune activation may occur with lamotrigine and that they Patients in the control group were intentionally treated with a relatively low dose of valproate; as such, the sole objective of this trial was to monstrate the effectiveness and safety of monotherapy with lamotrigine, and cannot be interpreted to imply the superiority of lamotrigine

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

Adjunctive Therapy with Lamotrigine in Adults with Partial-Onset Seizures

The effectiveness of lamotrigine as adjunctive therapy (added to othe The effectiveness of lamotrigine as adjunctive therapy (added to other AEDs) was initially established in 3 pivotal, multicenter

placebo-controlled, double-blind clinical trials in 355 adults with refractory partial-onset seizures. The patients had a history of at least 4 partial-onset seizures per month in spite of receiving 1 or more AEDs at therapeutic concentrations and in 2 of the trials were observed on their established AED regimen during baselines that varied between 8 to 12 weeks. In the third trial, patients were not observed in a 100-mg dose) by an average of 32% and 6%, respectively, and shortened the elimination half-lives by 27%. In the presence of attain an attain and in 2 of the trials were observed of attain attain attain attain attain attain an attain an attain an attain an attain and in 2 of the trials were observed of attain attain attain attain attain attain an attain a patients enrolled in efficacy trials.

One trial (n = 216) was a double-blind, placebo-controlled, parallel trial consisting of a 24-week treatment period. Patients could not be on more than 2 other anticonvulsants and valproate was not allowed. Patients were randomized to receive placebo, a target dose of 300 mg/day of lamotrique. The median reductions in the frequency of all partial-poset seizures relative to healthcare providers. healthcare providers.

for lamotrigine, or a target dose of 500 mg/day of lamotrigine. The median reductions in the frequency of all partial-onset seizures relative to baseline were 8% in patients receiving placebo, 20% in patients receiving 300 mg/day of lamotrigine, and 36% in patients receiving 500 mg/day of lamotrigine. The seizure frequency reduction was statistically significant in the 500-mg/day group compared with the placebo group, but not in the 300-mg/day group.

A second trial (n = 98) was a double-blind, placebo-controlled, randomized, crossover trial consisting of two 14-week treatment periods (the A second trial (n = 98) was a double-blind, placebo-controlled, randomized, crossover trial consisting of two 14-week treatment periods (the last 2 weeks of which consisted of dose tapering) separated by a 4-week washout period. Patients could not be on more than 2 other anticonvulsants and valproate was not allowed. The target dose of lamotrigine was 400 mg/day. When the first 12 weeks of the treatment anticonvulsants and valproate was not allowed. The target dose of lamotrigine was 400 mg/day. When the first 12 weeks of the treatment anticonvulsants and valproate was not allowed. The target dose of lamotrigine was 400 mg/day. When the first 12 weeks of the treatment anticonvulsants and valproate was not allowed. The target dose of lamotrigine was 400 mg/day. When the first 12 weeks of the treatment anticonvulsants and valproate was not allowed. The target dose of lamotrigine was 400 mg/day. When the first 12 weeks of the treatment anticonvulsants and valproate was not allowed. The target dose of lamotrigine was 400 mg/day. When the first 12 weeks of the treatment anticonvulsants and valproate was not allowed. The target dose of lamotrigine was 400 mg/day. When the first 12 weeks of the treatment periods (the properties of the treatment and the properties of the properties of the treatment and the proper periods were analyzed, the median change in seizure frequency was a 25% reduction on lamotrigine compared with placebo (P<0.001). The third trial (n = 41) was a double-blind, placebo-controlled, crossover trial consisting of two 12-week treatment periods separated by a 4-week washout period. Patients could not be on more than 2 other anticonvulsants. Thirteen patients were on concomitant valproate; these patients received 150 mg/day of lamotrigine. The 28 other patients had a target dose of 300 mg/day of lamotrigine. The median change in

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

The effectiveness of lamotrioine as adjunctive therapy in pediatric patients with partial-onset seizures was established in a multicenter, effects of this drug. Discuss the benefits and risks of continuing breastfeeding. double-blind, placebo-controlled trial in 199 patients aged 2 to 16 years (n = 98 on lamotrigine, n = 101 on placebo). Following an 8-week baseline phase, patients were randomized to 18 weeks of treatment with lamotrigine or placebo added to their current AED regimen of up to

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

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

lamotrigine and placebo, respectively). Adjunctive Therapy with Lamotrigine in Pediatric and Adult Patients with Primary Generalized Tonic-Clonic Seizures

The effectiveness of lamotrigine as adjunctive therapy in patients with PGTC seizures was established in a multicenter, double-blind, olacebo-controlled trial in 117 pediatric and adult patients aged 2 years and older (n = 58 on lamotrigine, n = 59 on placebo). Patients with at east 3 PGTC seizures during an 8-week baseline phase were randomized to 19 to 24 weeks of treatment with lamotrigine or placebo and 11 per placebo and 12 per placebo and 13 per placebo and 14 per placebo and 15 to their current AED regimen of up to 2 drugs. Patients were dosed on a fixed-dose regimen, with target doses ranging from 3 to 12 mg/kg/day for pediatric patients and from 200 to 400 mg/day for adult patients based on concomitant AEDs.

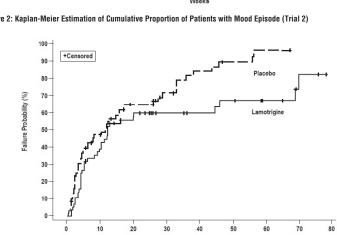
although the finding was more robust for depression.

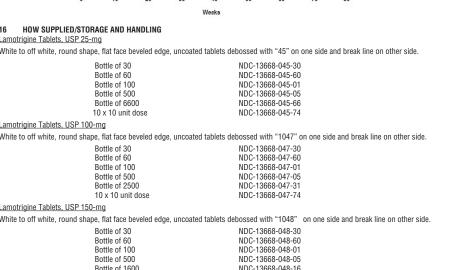
placebo-controlled trials in adult patients (aged 18 to 82 years) who met DSM-IV criteria for bipolar I disorder. Trial 1 enrolled patients with a current or recent (within 60 days) episode of mania or hypomania as defined by DSM-IV. Both trials included a cohort of patients (30% of 404 subjects in Trial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

> In both trials, patients were titrated to a target dose of 200 mg of lamotrigine as add-on therapy or as monotherapy with gradual withdrawal of any psychotropic medications during an 8- to 16-week open-label period. Overall 81% of 1,305 patients participating in the open-label period were receiving 1 or more other psychotropic medications, including benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), atypical antipsychotics (including olanzapine), valproate, or lithium, during titration of lamotrigine. Patients with a CGI-severity score of 3 or placebo-controlled double-blind treatment period for up to 18 months. The primary endpoint was TIME (time to intervention for a mood episode or one that was emerging, time to discontinuation for either an adverse event that was judged to be related to bipolar disorder, or for lack of efficacy). The mood episode could be depression, mania, hypomania, or a mixed episode. n Trial 1, patients received double-blind monotherapy with lamotrigine 50 mg/day (n = 50), lamotrigine 200 mg/day (n = 124), lamotrigine

In both trials, patients were titrated to a target dose of 200 mg of lamotrigine as add-on therapy or as monotherapy with gradual withdrawa

400 mg/day (n = 47), or placebo (n = 121), Lamotrigine (200- and 400-mg/day treatment groups combined) was superior to placebo in delaying the time to occurrence of a mood episode (Figure 1). Separate analyses of the 200- and 400-mg/day dose groups revealed no addec benefit from the higher dose. Although these trials were not designed to separately evaluate time to the occurrence of depression or mania, a combined analysis for the 2





9 x 10 unit dose NDC-13668-048-64 Lamotrigine Tablets, USP 200-mg NDC-13668-049-30 Bottle of 30 Bottle of 60 NDC-13668-049-60 Bottle of 100 Bottle of 500 NDC-13668-049-05 Bottle of 1300 NDC-13668-049-13 9 x 10 unit dose NDC-13668-049-64

Lamotrigine Tablets, USP Starter Kit for Patients Not Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate (Orange Kit). 13.1 Cardinogenesis, Mutagenesis, Mutagenesi mg/kg/day and 10 to 15 mg/kg/day, respectively. The highest doses tested are less than the human dose of 400 mg/day on a body surface 100-mg, white to off white, round shape, flat face beveled edge, uncoated tablets debossed with "1047" on one side and break line on other

NDC-13668-266-99

Lamotrigine Tablets, USP Starter Kit for Patients Taking Carbamazepine, Phenytoin, Phenobarbital, or Primidone and Not Taking Valproate 25-mg, white to off white, round shape, flat face beveled edge, uncoated tablets debossed with "45" on one side and break line on other side 100-mg, white to off white, round shape, flat face beveled edge, uncoated tablets debossed with "1047" on one side and break line on other side. and 14, 100-mg tablets

Encourage patients to enroll in the NAAED Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll-free number 1-888-233-2334 [see Use in Specific Populations (8.1)]. Inform patients who intend to breastfeed that lamotrigine is present in breast milk and advise them to monitor their child for potential adverse

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

Levetiracetam
Potential druo interactions between levetiracetam and lamotrigine were assessed by evaluating serum concentrations of both agents during the plasma concentrations of lamotrigine were not affected by concomitant lacosamide (200, 400, or 600 mg/day) in placebo-controlled clinical trials in patients were dosed based on body weight and valproate use. Target doses were designed to approximate 5 mg/kg/day for patients were dosed based on body weight and valproate (maximum dose: 250 mg/day). The perparations. Starting estrogen-containing oral contraceptives may significantly decrease lamotrigine plasma levels and stopping estrogen-containing oral contraceptives may significantly increase lamotrigine plasma levels (see Warnings and primary efficacy endpoint) and primary efficacy endpoint was percentage change from baseline in all partial-onset seizures was 36% in patients were andomized to 18 weeks of treatment with lamotrigine or placebo added on body weight and valproate use. Target doses were designed to approximate 5 mg/kg/day for patients were dosed based on body weight and valproate (maximum dose: 250 mg/day). The perparations. 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 primary efficacy endpoint was percentage change from baseline in all partial-onset seizures was 36% in patients treated with lamotrigine were assessed by evaluating serum concentrations of both agents during the pill-free week) may significantly increase lamotrigine plasma levels (see Warnings and primary efficacy endpoints).

**Total Contraceptives of the patients were dosed based on body weight and valproate (maximum dose: 250 mg/day). Th

Instruct patients to notify their healthcare providers if they become pregnant or intend to become pregnant during therapy and if they intend

Discontinuing Lamotrigine The effectiveness of lamotrigine as adjunctive therapy in patients with Lennox-Gastaut syndrome was established in a multicenter, double-blind, placebo-controlled trial in 169 patients aged 3 to 25 years (n = 79 on lamotrigine, n = 90 on placebo). Following a 4-week, consulting their healthcare providers if they stop taking lamotrigine for any reason and not to resume lamotrigine without consulting their healthcare providers. Aseptic Meningitis

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

should report signs or symptoms such as fever, rash, or lymphadenopathy to a healthcare provider immediately.

Multiorgan Hypersensitivity Reactions, Blood Dyscrasias, and Organ Failure

Cardiac Rhythm and Conduction Abnormalities

Central Nervous System Adverse Effects

to breastfeed or are breastfeeding an infant.

Pregnancy and Nursing

medications.

Prior to initiation of treatment with lamotrigine, inform patients that a rash or other signs or symptoms of hypersensitivity (e.g., fever,

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

Inform patients, their caregivers, and families that AEDs, including lamotrigine, may increase the risk of suicidal thoughts and behavior

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

are lamotrigine, as well as the correct formulation of lamotrigine, each time they fill their prescription [see Dosage Forms and Strengths (3.1), How Supplied/Storage and Handling (16)]. Refer the patient to the Medication Guide that provides depictions of the lamotrigine tablets. Dispense with Medication Guide available at: https://torrentpharma.com/pi/usa/products/

Torrent Pharmaceuticals LTD., India.

Torrent Pharma INC., Basking Ridge, NJ 07920.

Revised: August 2024

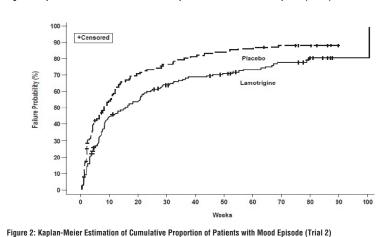


Figure 1: Kaplan-Meier Estimation of Cumulative Proportion of Patients with Mood Episode (Trial 1)

