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Practice limited to Domestic & International  
Pharmaceutical Patent Law  
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25 May 2005

The United States Food & Drug Administration  
Division of Dockets Management (HFA-305)  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852  
BY EXPRESS MAIL  
No. ER 000 849 905 US

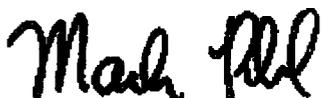
Re: Docket No. \_\_\_\_\_ (Suitability Petition for lamotrigine)

Dear Sirs :

Enclosed find the original and three copies of a SUITABILITY PETITION for a new dosage strength for the captioned drug product. Please let me know if you require any further information.

Many thanks in advance for your help.

With my very best regards,



J. Mark POHL  
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*Mark.Pohl@LicensingLaw.Net*

Mbc:mp  
Enclosure  
Cc w/enclosure :

Emily THAKUR, Office of Generic Drugs

2005 P. 0212

CP1

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*In re* Lamotrigine 50 milligram  
And 250 milligram oral tablets  
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**CITIZEN'S PETITION  
SUITABILITY PETITION**

This is a Suitability Petition submitted pursuant to 21 U.S.C. § 505(j)(2)(C) and 21 C.F.R. § 10.30.

Action Requested

This Petition requests the Commissioner of the Food & Drug Administration make a determination that:

- A. the drug product lamotrigine oral tablets, in the strength of 50 mg is suitable for consideration in an Abbreviated New Drug Application; and
- B. the drug product lamotrigine oral tablets, in the strength of 250 mg is suitable for consideration in an Abbreviated New Drug Application.

Statement of Grounds for Relief

The Reference Listed Drug

The reference listed drug product is Lamictal® brand lamotrigine oral tablets. The reference listed drug is an antiepileptic drug. See FDA approved labeling text for Lamictal® brand lamotrigine tablets and (NDA 20-241/S-017) (20 June 2003) at page 2, line 56 (copy enclosed). The reference listed drug is the subject of approved New Drug Application No. 20-241. The Holder is GlaxoSmithKline.

The NDA approval for the reference listed drug has not been withdrawn due to safety nor efficacy concerns. To the contrary, it was approved for use on 27 December 1994, and since that time has enjoyed a record of safety and effectiveness which supported its approval for additional labeled indications. *See* Paul Leber, Letter (14 Dec. 1998) (copy enclosed); Russell Katz, Letter (14 Jan 2004) (copy enclosed). It is currently approved for use as adjunctive therapy for partial seizures in adults and pediatric patients at least two years of age. *Id.* at page 13, lines 368 *et seq.* It is also approved for use as mono-therapy in adults, and for bipolar disorder maintenance. *Id.*

The approved dosing regimen requires that the drug dosage be adjusted to the patient's body weight. For example, epilepsy patients 2 to 12 years of age using valproate combination therapy require an initial daily dose of 0.15 mg per kilogram of patient body weight. *Id.* at page 38, Table 9. After two weeks, the recommended dosage increases to 0.3 mg per kilogram of body weight. *Id.* After four weeks, the recommended dosage increases to 1.0 to 5.0 mg per kilogram of body weight. *Id.*

Similarly, the approved dosages for bipolar patients not taking valproate range from a relatively low initial dose of 50 mg per day, and gradually increasing to a maintenance dose of up to 400 mg per day. *Id.* at page 41.

Similarly, to minimize adverse side effects, discontinuing use of this drug requires gradually reducing the dosage over time. *See id.*

Because the dosage must be adjusted over time, and must be adjusted to respond to the patient's body weight, the reference listed drug is currently available in four dosage strengths: 25 mg, 100 mg, 150 mg and 200 mg. *See* United States Food & Drug

Administration, Electronic Orange Book entry for Lamictal® brand lamotrigine oral tablets (20 May 2005) (copy attached).

The Proposed New Dosage Strength

An Abbreviated New Drug Application may be filed for the approval of a new drug product that is the same as the reference listed drug. 21 U.S.C.A. § 355(j)(2)(A) (2005). An Abbreviated New Drug Application may also be filed for a new drug product which is the same as the reference listed drug except for a difference in dosage strength, if the Commissioner grants permission to file such an Application by making an administrative finding that the difference in dosage form is suitable. See 21 U.S.C.A. § 355(j)(2)(C) (2005); 21 C.F.R. § 314.93(b). The Commissioner has authority to approve a Suitability Petition seeking a change in dosage strength. See 21 C.F.R. § 10.25, 10.30 (2005).

Petitioner respectfully requests the Commissioner make a determination that lamotrigine oral tablet drug product is suitable for consideration in an Abbreviated New Drug Application, in the strengths of 50 mg and 250 mg.

There is no reason to question the safety and effectiveness of the proposed drug products for their labeled uses. The reference listed drug was approved for use on 27 December 1994. Since that time, it has enjoyed a record of safety and effectiveness which supported its approval for additional labeled indications. See Paul Leber, Letter (14 Dec. 1998) (copy enclosed); Russell Katz, Letter (14 Jan 2004) (copy enclosed).

These proposed drug products will contain the same active drug substance as the reference listed drug, have the same route of administration (oral) as the reference listed drug, will have the same delivery mechanism (immediate release), and have the same dosage form (tablet). The labeling of the proposed drug product will also be the same as

the currently-approved labeling for the reference listed drug, except for changes which are required because of the difference in manufacturer and the difference in dosage form proposed under this Petition. The proposed products will differ from the reference listed drug only in their dosage strength.

Petitioner believes this change in dosage strength will reduce patient error by improving the ability of clinicians to prescribe precise amounts of the drug substance, and thereby reduce patient compliance error. This would appear especially important where, as here, the patient suffers from a neurological disorder which may impair the patient's ability to follow a complex dosing regimen. For example, asking a patient to take one 50 mg tablet appears less prone to error than asking the same patient to take two 25 mg tablets. Similarly, asking a patient to take one 250 mg tablet appears less prone to error than asking the same patient to take one 200 mg tablet and two 25 mg tablets; it does not appear overly difficult to imagine the patient mistakenly taking two 200 mg tablets and one 25 mg tablet, for an overdose of 425 mg, rather than the 250 mg intended.

Suitability of the 50 mg strength is respectfully believed warranted because the Food & Drug Administration routinely approves Suitability Petitions asking for a change in dosage strength, where there is no change in labeling, route of administration, active drug substance, et cetera.

Suitability of the 250 mg strength is also respectfully believed warranted because the 250 mg strength, while larger than the currently approved 200 mg strength, remains within the range of dosages recommended in the approved labeling. The approved labeling recommends dosages up to 400 mg per day. *See* FDA approved labeling text for Lamictal® brand lamotrigine tablets and (NDA 20-241/S-017 (20 June 2003) at page 42,

Table 14, right-hand column. Thus, the proposed 250 mg strength is well within the range of currently-approved dosages.

The record of this product before the Food & Drug Administration includes a problem with prescription-fulfillment. Specifically, in 2000, the Holder issued “Dear Doctor” and “Dear Pharmacist” letters, warning of potential confusion between the trademark for the reference listed drug - Lamictal® - and the trademark Lamisil®, used for an unrelated antifungal drug. *See* N. Scott Sykes, Letter (6 June 2000); N. Scott Sykes, Letter (July 2000); Richard S. Kent, Letter (August, 2000) (copies enclosed).

Petitioner respectfully notes that the proposed products are generic forms of the reference listed drug. These generic products will therefore not carry the potentially-confusing Lamictal® trademark. Therefore, the proposed generic products thus appear safer in this regard than the reference listed drug. There thus appears no reason to question the safety and efficacy of these products.

For the foregoing reasons, Petitioner respectfully believes that the proposed dosages are suitable for approval under an Abbreviated New Drug Application.

#### Request to Waive Pediatric Assessment

An assessment of the safety and efficacy of the product in pediatric patients is required for any application for a new active ingredient, dosage form, indication, route of administration or dosing regimen. *See* 21 U.S.C. § 355B(A)(4)(ii) (2004).

This Petition does not request any change in active ingredient, dosage form, indication, route of administration, nor dosing regimen. The dosing regimen – the amount of drug the patient will be administered, and when, and for what symptoms, and with what co-administered therapeutics - will remain the same as the dosing regimen

currently-approved for the reference listed drug. This Petition proposes changing the strength of the individual tablets, not the drug dosing regimen which those tablets are used for. Petitioner therefore respectfully believes that this Petition does not require pediatric assessment.

In the alternative, Petitioner requests waiver of pediatric assessment, because the Agency has waived and deferred the pediatric assessments for the reference listed drug. *See* Russell KATZ, Letter at page 2 (14 January 2004) (“We are waiving the pediatric study requirement for ages 0 years up to 1 month of age and deferring pediatric studies for ages 1 month to 16 years for” the reference listed drug).

Petitioner therefore respectfully believes that a full waiver of pediatric studies is warranted.

Environmental Impact

Petitioner respectfully believes that it need not submit environmental impact information, because such information is categorically excluded from Suitability Petitions. *See* 21 C.F.R. § 25.31.

Economic Impact

Petitioner respectfully believes that it need not submit economic impact information unless requested to do so by the Commissioner. *See* 21 C.F.R. § 10.30(b).

Action Requested

Petitioner respectfully requests the Commissioner make a determination that:

- A. the drug product lamotrigine oral tablets, in the strength of 50 mg is suitable for consideration in an Abbreviated New Drug Application; and

B. the drug product lamotrigine oral tablets, in the strength of 250 mg is suitable for consideration in an Abbreviated New Drug Application.

Petitioner also requests the Commissioner to make a determination that these tablet strengths are either exempt from the requirement for pediatric assessment, or that are subject to assessment and the requirement is waived.

Certification

The undersigned certifies that, to the best of their knowledge and belief, this Suitability Petition includes all information and views upon which the Petition relies, and includes representative data and information known to Petitioner which are unfavorable to this Petition.

Respectfully Submitted,  
PHARMACEUTICAL PATENT ATTORNEYS, LLC

B  
M  
53

A black rectangular box containing a handwritten signature in white ink that reads "J. Mark All". A horizontal line extends from the right side of the box.

Morristown, NJ 07960-7397  
Direct Dial (973) 984-0076

Enclosures

Enclosures

- 1) Draft "How Supplied" section of product insert for proposed new dosage strength.
- 2) FDA approved labeling text for Lamictal® brand lamotrigine tablets and (NDA 20-241/S-017 (20 June 2003).
- 3) Russell Katz, Letter (14 Jan 2004).
- 4) Paul Leber, Letter (14 Dec. 1998)
- 5) N. Scott Sykes, Letter (6 June 2000); N. Scott Sykes, Letter (July 2000); Richard S. Kent, Letter (August, 2000).
- 6) United States Food & Drug Administration, Electronic Orange Book entry for Lamictal® brand lamotrigine oral tablets (20 May 2005).

Draft "How Supplied" section of product insert for proposed new dosage strength

**HOW SUPPLIED:**

**Lamotrigine tablets 25 mg are white to off-white, round, flat, beveled edged tablets with bisect on one side; one side of the bisect is debossed with logo of "ZC" and other side is debossed with "79" and other side is plain and are supplied as follows**

**NDC-68382-006-11 in bottles of 25 tablets  
NDC-68382-006-16 in bottles of 90 tablets  
NDC-68382-006-01 in bottles of 100 tablets  
NDC-68382-006-05 in bottles of 500 tablets  
NDC-68382-006-10 in bottles of 1000 tablets**

**Lamotrigine tablets 50 mg are white to off-white, round, flat, beveled edged tablets with bisect on one side; one side of the bisect is debossed with logo of "ZC" and other side is debossed with "90" and other side is plain and are supplied as follows**

**NDC-68382-007-16 in bottles of 90 tablets  
NDC-68382-007-01 in bottles of 100 tablets  
NDC-68382-007-05 in bottles of 500 tablets  
NDC-68382-007-10 in bottles of 1000 tablets**

**Lamotrigine tablets 100 mg are white to off-white, round, flat, beveled edged tablets with bisect on one side; one side of the bisect is debossed with logo of "ZC" and other side is debossed with "80" and other side is plain and are supplied as follows**

**NDC-68382-008-16 in bottles of 90 tablets  
NDC-68382-008-01 in bottles of 100 tablets  
NDC-68382-008-05 in bottles of 500 tablets  
NDC-68382-008-10 in bottles of 1000 tablets**

**Lamotrigine tablets 150 mg are white to off-white, round, flat, beveled edged tablets with bisect on one side; one side of the bisect is debossed with logo of "ZC" and other side is debossed with "81" and other side is plain and are supplied as follows**

**NDC-68382-009-14 in bottles of 60 tablets  
NDC-68382-009-16 in bottles of 90 tablets  
NDC-68382-009-05 in bottles of 500 tablets**

**Lamotrigine tablets 200 mg are white to off-white, round, flat, beveled edged tablets with bisect on one side; one side of the bisect is debossed with logo of "ZC" and other side is debossed with "82" and other side is plain and are supplied as follows**

**NDC-68382-010-14 in bottles of 60 tablets**

**NDC-68382-010-16 in bottles of 90 tablets**

**NDC-68382-010-05 in bottles of 500 tablets**

**Lamotrigine tablets 250 mg are white to off-white, round, flat, beveled edged tablets with bisect on one side; one side of the bisect is debossed with logo of "ZC" and other side is debossed with "91" and other side is plain and are supplied as follows**

**NDC-68382-011-14 in bottles of 60 tablets**

**NDC-68382-011-16 in bottles of 90 tablets**

**NDC-68382-011-05 in bottles of 500 tablets**



Food and Drug Administration  
Rockville MD 20857

NDA 20-241/S-003  
NDA 20-764/S-001

DEC 14 1998

Glaxo Wellcome Inc.  
Attention: Elizabeth A. McConnell, Pharm.D.  
Project Director, Regulatory Affairs  
Five Moore Drive  
P.O. Box 13398  
Research Triangle Park, NC 27709

Dear Dr. McConnell:

Please refer to your supplemental new drug applications dated February 24, 1997 (NDA 20-241/S-003), and September 4, 1998 (NDA 20-764/S-001), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lamictal (lamotrigine) Tablets and Lamictal (lamotrigine) Chewable Dispersible Tablets.

We acknowledge receipt of your additional amendment to these supplemental applications dated October 20, 1998.

These supplemental new drug applications provide for the use of Lamictal (lamotrigine) Tablets and Lamictal (lamotrigine) Chewable Dispersible Tablets as conversion to monotherapy in adults with partial seizures who are receiving treatment with a single enzyme-inducing anti-epileptic drug (EIAED).

We have completed the review of these supplemental applications, as amended, and have *concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the enclosed labeling text.* Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Marketing the products with FPL that is not identical to the approved labeling text may render the products misbranded and unapproved new drugs.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 20-241/S-003, 20-764/S-001." Approval of these submissions by FDA is not required before the labeling is used.

NDA 20-241/S-003

NDA 20-764/S-001

Page 2

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

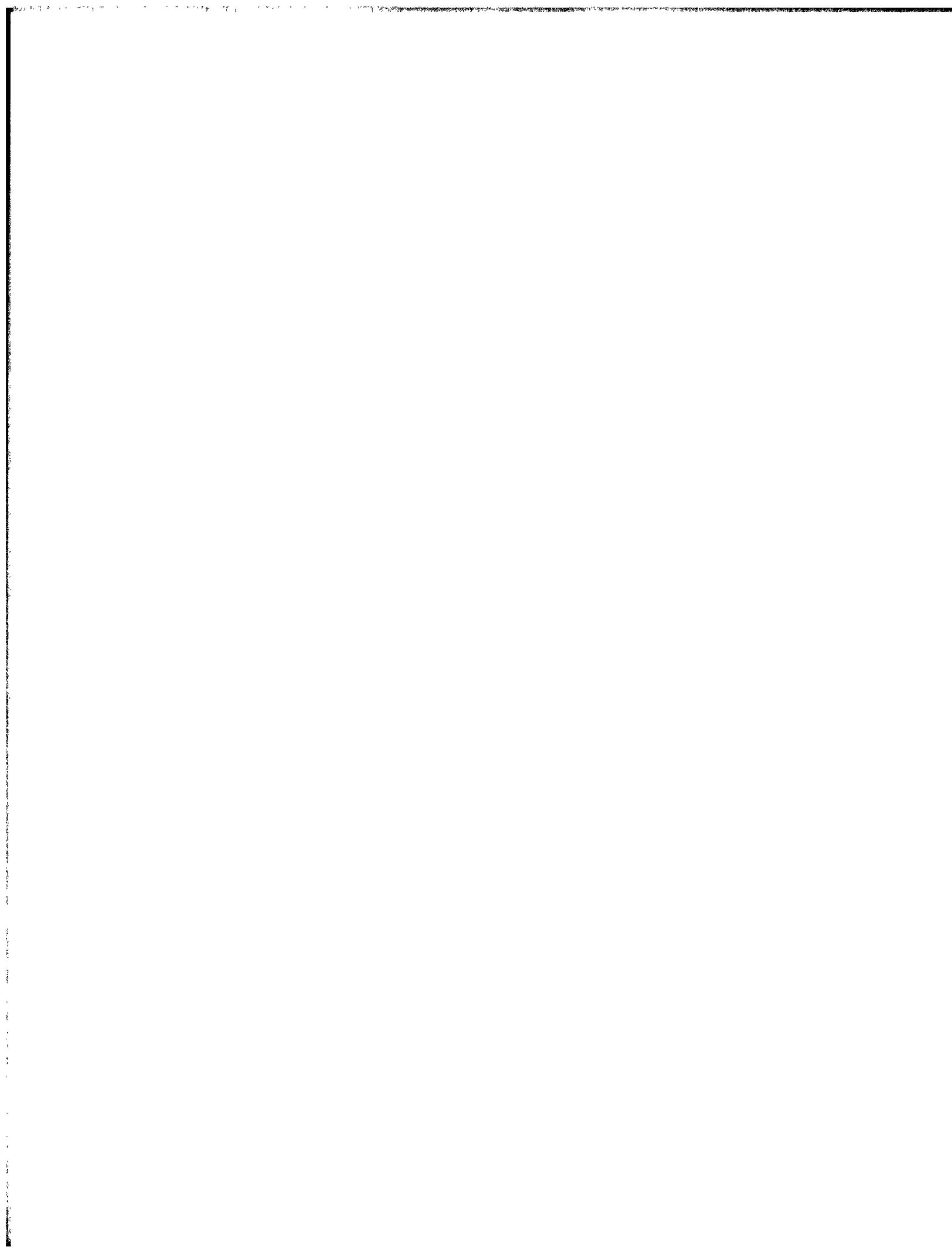
If you have any questions, contact Jacqueline H. Ware, Pharm.D., Regulatory Management Officer, at (301) 594-2850.

Sincerely yours,

/s/

Paul Leber, M.D.  
Director  
Division of Neuropharmacological Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure



**PRESCRIBING INFORMATION**

1  
2 **LAMICTAL<sup>®</sup>**  
3 **(lamotrigine)**  
4 **Tablets**

5  
6 **LAMICTAL<sup>®</sup>**  
7 **(lamotrigine)**  
8 **Chewable Dispersible Tablets**

9  
10 **SERIOUS RASHES REQUIRING HOSPITALIZATION AND DISCONTINUATION**  
11 **OF TREATMENT HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF**  
12 **LAMICTAL. THE INCIDENCE OF THESE RASHES, WHICH HAVE INCLUDED**  
13 **STEVENS-JOHNSON SYNDROME, IS APPROXIMATELY 0.8% (8 PER 1,000) IN**  
14 **PEDIATRIC PATIENTS (AGE <16 YEARS) RECEIVING LAMICTAL AS**  
15 **ADJUNCTIVE THERAPY FOR EPILEPSY AND 0.3% (3 PER 1,000) IN ADULTS ON**  
16 **ADJUNCTIVE THERAPY FOR EPILEPSY. IN CLINICAL TRIALS OF BIPOLAR AND**  
17 **OTHER MOOD DISORDERS, THE RATE OF SERIOUS RASH WAS 0.08% (0.8 PER**  
18 **1,000) IN ADULT PATIENTS RECEIVING LAMICTAL AS INITIAL MONOTHERAPY**  
19 **AND 0.13% (1.3 PER 1,000) IN ADULT PATIENTS RECEIVING LAMICTAL AS**  
20 **ADJUNCTIVE THERAPY. IN A PROSPECTIVELY FOLLOWED COHORT OF**  
21 **1,983 PEDIATRIC PATIENTS WITH EPILEPSY TAKING ADJUNCTIVE LAMICTAL,**  
22 **THERE WAS 1 RASH-RELATED DEATH. IN WORLDWIDE POSTMARKETING**  
23 **EXPERIENCE, RARE CASES OF TOXIC EPIDERMAL NECROLYSIS AND/OR**  
24 **RASH-RELATED DEATH HAVE BEEN REPORTED IN ADULT AND PEDIATRIC**  
25 **PATIENTS, BUT THEIR NUMBERS ARE TOO FEW TO PERMIT A PRECISE**  
26 **ESTIMATE OF THE RATE.**

27 **BECAUSE THE RATE OF SERIOUS RASH IS GREATER IN PEDIATRIC**  
28 **PATIENTS THAN IN ADULTS, IT BEARS EMPHASIS THAT LAMICTAL IS**  
29 **APPROVED ONLY FOR USE IN PEDIATRIC PATIENTS BELOW THE AGE OF**  
30 **16 YEARS WHO HAVE SEIZURES ASSOCIATED WITH THE LENNOX-GASTAUT**  
31 **SYNDROME OR IN PATIENTS WITH PARTIAL SEIZURES (SEE INDICATIONS).**

32 **OTHER THAN AGE, THERE ARE AS YET NO FACTORS IDENTIFIED THAT ARE**  
33 **KNOWN TO PREDICT THE RISK OF OCCURRENCE OR THE SEVERITY OF RASH**  
34 **ASSOCIATED WITH LAMICTAL. THERE ARE SUGGESTIONS, YET TO BE**  
35 **PROVEN, THAT THE RISK OF RASH MAY ALSO BE INCREASED BY (1)**  
36 **COADMINISTRATION OF LAMICTAL WITH VALPROATE (INCLUDES VALPROIC**  
37 **ACID AND DIVALPROEX SODIUM), (2) EXCEEDING THE RECOMMENDED**  
38 **INITIAL DOSE OF LAMICTAL, OR (3) EXCEEDING THE RECOMMENDED DOSE**

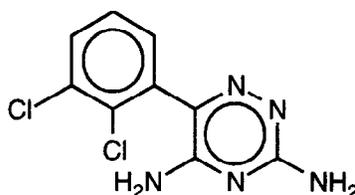
39 **ESCALATION FOR LAMICTAL. HOWEVER, CASES HAVE BEEN REPORTED IN**  
40 **THE ABSENCE OF THESE FACTORS.**

41 **NEARLY ALL CASES OF LIFE-THREATENING RASHES ASSOCIATED WITH**  
42 **LAMICTAL HAVE OCCURRED WITHIN 2 TO 8 WEEKS OF TREATMENT**  
43 **INITIATION. HOWEVER, ISOLATED CASES HAVE BEEN REPORTED AFTER**  
44 **PROLONGED TREATMENT (e.g., 6 MONTHS). ACCORDINGLY, DURATION OF**  
45 **THERAPY CANNOT BE RELIED UPON AS A MEANS TO PREDICT THE**  
46 **POTENTIAL RISK HERALDED BY THE FIRST APPEARANCE OF A RASH.**

47 **ALTHOUGH BENIGN RASHES ALSO OCCUR WITH LAMICTAL, IT IS NOT**  
48 **POSSIBLE TO PREDICT RELIABLY WHICH RASHES WILL PROVE TO BE**  
49 **SERIOUS OR LIFE THREATENING. ACCORDINGLY, LAMICTAL SHOULD**  
50 **ORDINARILY BE DISCONTINUED AT THE FIRST SIGN OF RASH, UNLESS THE**  
51 **RASH IS CLEARLY NOT DRUG RELATED. DISCONTINUATION OF TREATMENT**  
52 **MAY NOT PREVENT A RASH FROM BECOMING LIFE THREATENING OR**  
53 **PERMANENTLY DISABLING OR DISFIGURING.**

## 54 **DESCRIPTION**

55 LAMICTAL (lamotrigine), an antiepileptic drug (AED) of the phenyltriazine class, is  
56 chemically unrelated to existing antiepileptic drugs. Its chemical name is 3,5-diamino-6-(2,3-  
57 dichlorophenyl)-*as*-triazine, its molecular formula is  $C_9H_7N_5Cl_2$ , and its molecular weight is  
58 256.09. Lamotrigine is a white to pale cream-colored powder and has a  $pK_a$  of 5.7. Lamotrigine  
59 is very slightly soluble in water (0.17 mg/mL at 25°C) and slightly soluble in 0.1 M HCl  
60 (4.1 mg/mL at 25°C). The structural formula is:



63  
64  
65 LAMICTAL Tablets are supplied for oral administration as 25-mg (white), 100-mg (peach),  
66 150-mg (cream), and 200-mg (blue) tablets. Each tablet contains the labeled amount of  
67 lamotrigine and the following inactive ingredients: lactose; magnesium stearate; microcrystalline  
68 cellulose; povidone; sodium starch glycolate; FD&C Yellow No. 6 Lake (100-mg tablet only);  
69 ferric oxide, yellow (150-mg tablet only); and FD&C Blue No. 2 Lake (200-mg tablet only).

70 LAMICTAL Chewable Dispersible Tablets are supplied for oral administration. The tablets  
71 contain 2 mg (white), 5 mg (white), or 25 mg (white) of lamotrigine and the following inactive  
72 ingredients: blackcurrant flavor, calcium carbonate, low-substituted hydroxypropylcellulose,  
73 magnesium aluminum silicate, magnesium stearate, povidone, saccharin sodium, and sodium

74 starch glycolate.

75

## 76 **CLINICAL PHARMACOLOGY**

77 **Mechanism of Action:** The precise mechanism(s) by which lamotrigine exerts its  
78 anticonvulsant action are unknown. In animal models designed to detect anticonvulsant activity,  
79 lamotrigine was effective in preventing seizure spread in the maximum electroshock (MES) and  
80 pentylenetetrazol (scMet) tests, and prevented seizures in the visually and electrically evoked  
81 after-discharge (EEAD) tests for antiepileptic activity. The relevance of these models to human  
82 epilepsy, however, is not known.

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

88 The mechanisms by which lamotrigine exerts its therapeutic action in Bipolar Disorder have  
89 not been established.

90 **Pharmacological Properties:** Although the relevance for human use is unknown, the  
91 following data characterize the performance of LAMICTAL in receptor binding assays.  
92 Lamotrigine had a weak inhibitory effect on the serotonin 5-HT<sub>3</sub> receptor (IC<sub>50</sub> = 18 μM). It does  
93 not exhibit high affinity binding (IC<sub>50</sub>>100 μM) to the following neurotransmitter receptors:  
94 adenosine A<sub>1</sub> and A<sub>2</sub>; adrenergic α<sub>1</sub>, α<sub>2</sub>, and β; dopamine D<sub>1</sub> and D<sub>2</sub>; γ-aminobutyric acid  
95 (GABA) A and B; histamine H<sub>1</sub>; kappa opioid; muscarinic acetylcholine; and serotonin 5-HT<sub>2</sub>.  
96 Studies have failed to detect an effect of lamotrigine on dihydropyridine-sensitive calcium  
97 channels. It had weak effects at sigma opioid receptors (IC<sub>50</sub> = 145 μM). Lamotrigine did not  
98 inhibit the uptake of norepinephrine, dopamine, or serotonin (IC<sub>50</sub>>200 μM) when tested in rat  
99 synaptosomes and/or human platelets in vitro.

### 100 ***Effect of Lamotrigine on N-Methyl d-Aspartate-Receptor Mediated Activity:***

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

106 ***Folate Metabolism:*** In vitro, lamotrigine was shown to be an inhibitor of dihydrofolate  
107 reductase, the enzyme that catalyzes the reduction of dihydrofolate to tetrahydrofolate. Inhibition  
108 of this enzyme may interfere with the biosynthesis of nucleic acids and proteins. When oral daily  
109 doses of lamotrigine were given to pregnant rats during organogenesis, fetal, placental, and  
110 maternal folate concentrations were reduced. Significantly reduced concentrations of folate are  
111 associated with teratogenesis (see PRECAUTIONS: Pregnancy). Folate concentrations were also  
112 reduced in male rats given repeated oral doses of lamotrigine. Reduced concentrations were

113 partially returned to normal when supplemented with folic acid.

114 **Accumulation in Kidneys:** Lamotrigine was found to accumulate in the kidney of the male  
115 rat, causing chronic progressive nephrosis, necrosis, and mineralization. These findings are  
116 attributed to  $\alpha$ -2 microglobulin, a species- and sex-specific protein that has not been detected in  
117 humans or other animal species.

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

120 **Cardiovascular:** In dogs, lamotrigine is extensively metabolized to a 2-N-methyl  
121 metabolite. This metabolite causes dose-dependent prolongations of the PR interval, widening of  
122 the QRS complex, and, at higher doses, complete AV conduction block. Similar cardiovascular  
123 effects are not anticipated in humans because only trace amounts of the 2-N-methyl metabolite  
124 (<0.6% of lamotrigine dose) have been found in human urine (see Drug Disposition below).  
125 However, it is conceivable that plasma concentrations of this metabolite could be increased in  
126 patients with a reduced capacity to glucuronidate lamotrigine (e.g., in patients with liver disease).

127 **Pharmacokinetics and Drug Metabolism:** The pharmacokinetics of lamotrigine have been  
128 studied in patients with epilepsy, healthy young and elderly volunteers, and volunteers with  
129 chronic renal failure. Lamotrigine pharmacokinetic parameters for adult and pediatric patients  
130 and healthy normal volunteers are summarized in Tables 1 and 2.

131

132 **Table 1. Mean\* Pharmacokinetic Parameters in Healthy Volunteers and Adult Patients**  
 133 **With Epilepsy**

Adult Study Population	Number of Subjects	T <sub>max</sub> : Time of Maximum Plasma Concentration (h)	t <sub>1/2</sub> : Elimination Half-life (h)	Cl/F: Apparent Plasma Clearance (mL/min/kg)
Healthy volunteers taking no other medications:				
Single-dose LAMICTAL	179	2.2 (0.25-12.0)	32.8 (14.0-103.0)	0.44 (0.12-1.10)
Multiple-dose LAMICTAL	36	1.7 (0.5-4.0)	25.4 (11.6-61.6)	0.58 (0.24-1.15)
Healthy volunteers taking valproate:				
Single-dose LAMICTAL	6	1.8 (1.0-4.0)	48.3 (31.5-88.6)	0.30 (0.14-0.42)
Multiple-dose LAMICTAL	18	1.9 (0.5-3.5)	70.3 (41.9-113.5)	0.18 (0.12-0.33)
Patients with epilepsy taking valproate only:				
Single-dose LAMICTAL	4	4.8 (1.8-8.4)	58.8 (30.5-88.8)	0.28 (0.16-0.40)
Patients with epilepsy taking enzyme-inducing antiepileptic drugs (EIAEDs) <sup>†</sup> plus valproate:				
Single-dose LAMICTAL	25	3.8 (1.0-10.0)	27.2 (11.2-51.6)	0.53 (0.27-1.04)
Patients with epilepsy taking EIAEDs:				
Single-dose LAMICTAL	24	2.3 (0.5-5.0)	14.4 (6.4-30.4)	1.10 (0.51-2.22)
Multiple-dose LAMICTAL	17	2.0 (0.75-5.93)	12.6 (7.5-23.1)	1.21 (0.66-1.82)

134 \*The majority of parameter means determined in each study had coefficients of variation  
135 between 20% and 40% for half-life and C<sub>1</sub>/F and between 30% and 70% for T<sub>max</sub>. The overall  
136 mean values were calculated from individual study means that were weighted based on the  
137 number of volunteers/patients in each study. The numbers in parentheses below each parameter  
138 mean represent the range of individual volunteer/patient values across studies.

139 †Examples of EIAEDs are carbamazepine, phenobarbital, phenytoin, and primidone.

140

141 **Absorption:** Lamotrigine is rapidly and completely absorbed after oral administration with  
142 negligible first-pass metabolism (absolute bioavailability is 98%). The bioavailability is not  
143 affected by food. Peak plasma concentrations occur anywhere from 1.4 to 4.8 hours following  
144 drug administration. The lamotrigine chewable/dispersible tablets were found to be equivalent,  
145 whether they were administered as dispersed in water, chewed and swallowed, or swallowed as  
146 whole, to the lamotrigine compressed tablets in terms of rate and extent of absorption.

147 **Distribution:** Estimates of the mean apparent volume of distribution (V<sub>d</sub>/F) of lamotrigine  
148 following oral administration ranged from 0.9 to 1.3 L/kg. V<sub>d</sub>/F is independent of dose and is  
149 similar following single and multiple doses in both patients with epilepsy and in healthy  
150 volunteers.

151 **Protein Binding:** Data from in vitro studies indicate that lamotrigine is approximately 55%  
152 bound to human plasma proteins at plasma lamotrigine concentrations from 1 to 10 mcg/mL  
153 (10 mcg/mL is 4 to 6 times the trough plasma concentration observed in the controlled efficacy  
154 trials). Because lamotrigine is not highly bound to plasma proteins, clinically significant  
155 interactions with other drugs through competition for protein binding sites are unlikely. The  
156 binding of lamotrigine to plasma proteins did not change in the presence of therapeutic  
157 concentrations of phenytoin, phenobarbital, or valproate. Lamotrigine did not displace other  
158 AEDs (carbamazepine, phenytoin, phenobarbital) from protein binding sites.

159 **Drug Disposition:** Lamotrigine is metabolized predominantly by glucuronic acid  
160 conjugation; the major metabolite is an inactive 2-N-glucuronide conjugate. After oral  
161 administration of 240 mg of <sup>14</sup>C-lamotrigine (15 μCi) to 6 healthy volunteers, 94% was  
162 recovered in the urine and 2% was recovered in the feces. The radioactivity in the urine consisted  
163 of unchanged lamotrigine (10%), the 2-N-glucuronide (76%), a 5-N-glucuronide (10%), a  
164 2-N-methyl metabolite (0.14%), and other unidentified minor metabolites (4%).

165 **Drug Interactions:** The apparent clearance of lamotrigine is affected by the  
166 coadministration of AEDs. Lamotrigine is eliminated more rapidly in patients who have been  
167 taking hepatic EIAEDs, including carbamazepine, phenytoin, phenobarbital, and primidone.  
168 Most clinical experience is derived from this population.

169 **Valproate decreases the apparent clearance of lamotrigine (i.e., more than doubles the  
170 elimination half-life of lamotrigine), whether given with or without EIAEDs.** Accordingly, if  
171 lamotrigine is to be administered to a patient receiving valproate, lamotrigine must be given at a  
172 reduced dosage, no more than half the dose used in patients not receiving valproate (see

173 DOSAGE AND ADMINISTRATION and PRECAUTIONS: Drug Interactions).

174 In vitro inhibition experiments indicated that the formation of the primary metabolite of  
175 lamotrigine, the 2-N-glucuronide, was not significantly affected by co-incubation with clozapine,  
176 fluoxetine, phenelzine, risperidone, sertraline, or trazodone, and was minimally affected by co-  
177 incubation with amitriptyline, bupropion, clonazepam, haloperidol, or lorazepam. In addition,  
178 bufuralol metabolism data from human liver microsomes suggested that lamotrigine does not  
179 inhibit the metabolism of drugs eliminated predominantly by CYP2D6.

180 LAMICTAL has no effects on the pharmacokinetics of lithium (see PRECAUTIONS: Drug  
181 Interactions).

182 The pharmacokinetics of LAMICTAL were not changed by co-administration of bupropion  
183 (see PRECAUTIONS: Drug Interactions).

184 **Enzyme Induction:** The effects of lamotrigine on the induction of specific families of  
185 mixed-function oxidase isozymes have not been systematically evaluated.

186 Following multiple administrations (150 mg twice daily) to normal volunteers taking no other  
187 medications, lamotrigine induced its own metabolism, resulting in a 25% decrease in  $t_{1/2}$  and a  
188 37% increase in Cl/F at steady state compared to values obtained in the same volunteers  
189 following a single dose. Evidence gathered from other sources suggests that self-induction by  
190 LAMICTAL may not occur when LAMICTAL is given as adjunctive therapy in patients  
191 receiving EIAEDs.

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

198 **Elimination:** (see Table 1).

199 **Special Populations: Patients With Renal Insufficiency:** Twelve volunteers with  
200 chronic renal failure (mean creatinine clearance = 13 mL/min; range = 6 to 23) and another  
201 6 individuals undergoing hemodialysis were each given a single 100-mg dose of LAMICTAL.  
202 The mean plasma half-lives determined in the study were 42.9 hours (chronic renal failure),  
203 13.0 hours (during hemodialysis), and 57.4 hours (between hemodialysis) compared to  
204 26.2 hours in healthy volunteers. On average, approximately 20% (range = 5.6 to 35.1) of the  
205 amount of lamotrigine present in the body was eliminated by hemodialysis during a 4-hour  
206 session.

207 **Hepatic Disease:** The pharmacokinetics parameters of lamotrigine in patients with  
208 impaired liver function have not been studied.

209 **Age: Pediatric Patients:** The pharmacokinetics of LAMICTAL following a single 2-mg/kg  
210 dose were evaluated in 2 studies of pediatric patients (n = 29 for patients aged 10 months to 5.9  
211 years and n = 26 for patients aged 5 to 11 years). Forty-three patients received concomitant

212 therapy with other AEDS and 12 patients received LAMICTAL as monotherapy. Lamotrigine  
213 pharmacokinetic parameters for pediatric patients are summarized in Table 2.

214 Population pharmacokinetic analyses involving patients aged 2 to 18 years demonstrated that  
215 lamotrigine clearance was influenced predominantly by total body weight and concurrent AED  
216 therapy. The oral clearance of lamotrigine was higher, on a body weight basis, in pediatric  
217 patients than in adults. Weight-normalized lamotrigine clearance was higher in those subjects  
218 weighing less than 30 kg, compared with those weighing greater than 30 kg. Accordingly,  
219 patients weighing less than 30 kg may need an increase of as much as 50% in maintenance doses,  
220 based on clinical response, as compared with subjects weighing more than 30 kg being  
221 administered the same AEDs (see DOSAGE AND ADMINISTRATION). These analyses also  
222 revealed that, after accounting for body weight, lamotrigine clearance was not significantly  
223 influenced by age. Thus, the same weight-adjusted doses should be administered to children  
224 irrespective of differences in age. Concomitant AEDs which influence lamotrigine clearance in  
225 adults were found to have similar effects in children.

226

227 **Table 2. Mean Pharmacokinetic Parameters in Pediatric Patients With Epilepsy**

Pediatric Study Population	Number of Subjects	T <sub>max</sub> (h)	t <sub>½</sub> (h)	Cl/F (mL/min/kg)
<b>Ages 10 months-5.3 years</b>				
Patients taking enzyme-inducing antiepileptic drugs (EIAEDs)	10	3.0 (1.0-5.9)	7.7 (5.7-11.4)	3.62 (2.44-5.28)
Patients taking antiepileptic drugs (AEDs) with no known effect on drug-metabolizing enzymes	7	5.2 (2.9-6.1)	19.0 (12.9-27.1)	1.2 (0.75-2.42)
Patients taking valproate only	8	2.9 (1.0-6.0)	44.9 (29.5-52.5)	0.47 (0.23-0.77)
<b>Ages 5-11 years</b>				
Patients taking EIAEDs	7	1.6 (1.0-3.0)	7.0 (3.8-9.8)	2.54 (1.35-5.58)
Patients taking EIAEDs plus valproate	8	3.3 (1.0-6.4)	19.1 (7.0-31.2)	0.89 (0.39-1.93)
Patients taking valproate only*	3	4.5 (3.0-6.0)	65.8 (50.7-73.7)	0.24 (0.21-0.26)
<b>Ages 13-18 years</b>				
Patients taking EIAEDs	11	†	†	1.3
Patients taking EIAEDs plus valproate	8	†	†	0.5
Patients taking valproate only	4	†	†	0.3

228 \*Two subjects were included in the calculation for mean T<sub>max</sub>.

229 † Parameter not estimated.

230

231 **Elderly:** The pharmacokinetics of lamotrigine following a single 150-mg dose of  
 232 LAMICTAL were evaluated in 12 elderly volunteers between the ages of 65 and 76 years (mean  
 233 creatinine clearance = 61 mL/min, range = 33 to 108 mL/min). The mean half-life of lamotrigine  
 234 in these subjects was 31.2 hours (range, 24.5 to 43.4 hours), and the mean clearance was  
 235 0.40 mL/min/kg (range, 0.26 to 0.48 mL/min/kg).

236 **Gender:** The clearance of lamotrigine is not affected by gender.

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

239

240 **CLINICAL STUDIES**

241 **Epilepsy:** The results of controlled clinical trials established the efficacy of LAMICTAL as  
242 monotherapy in adults with partial onset seizures already receiving treatment with a single  
243 enzyme-inducing antiepileptic drug (EIAED), as adjunctive therapy in adults and pediatric  
244 patients age 2 to 16 with partial seizures, and as adjunctive therapy in the generalized seizures of  
245 Lennox-Gastaut syndrome in pediatric and adult patients.

246 ***Monotherapy With LAMICTAL in Adults With Partial Seizures Already Receiving***  
247 ***Treatment With a Single EIAED:*** The effectiveness of monotherapy with LAMICTAL was  
248 established in a multicenter, double-blind clinical trial enrolling 156 adult outpatients with partial  
249 seizures. The patients experienced at least 4 simple partial, complex partial, and/or secondarily  
250 generalized seizures during each of 2 consecutive 4-week periods while receiving carbamazepine  
251 or phenytoin monotherapy during baseline. LAMICTAL (target dose of 500 mg/day) or valproate  
252 (1,000 mg/day) was added to either carbamazepine or phenytoin monotherapy over a 4-week  
253 period. Patients were then converted to monotherapy with LAMICTAL or valproate during the  
254 next 4 weeks, then continued on monotherapy for an additional 12-week period.

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

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

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

270 ***Adjunctive Therapy With LAMICTAL in Adults With Partial Seizures:*** The  
271 effectiveness of LAMICTAL as adjunctive therapy (added to other AEDs) was established in  
272 3 multicenter, placebo-controlled, double-blind clinical trials in 355 adults with refractory partial  
273 seizures. The patients had a history of at least 4 partial seizures per month in spite of receiving  
274 one or more AEDs at therapeutic concentrations and, in 2 of the studies, were observed on their  
275 established AED regimen during baselines that varied between 8 to 12 weeks. In the third,  
276 patients were not observed in a prospective baseline. In patients continuing to have at least 4  
277 seizures per month during the baseline, LAMICTAL or placebo was then added to the existing  
278 therapy. In all 3 studies, change from baseline in seizure frequency was the primary measure of  
279 effectiveness. The results given below are for all partial seizures in the intent-to-treat population

280 (all patients who received at least one dose of treatment) in each study, unless otherwise  
281 indicated. The median seizure frequency at baseline was 3 per week while the mean at baseline  
282 was 6.6 per week for all patients enrolled in efficacy studies.

283 One study (n = 216) was a double-blind, placebo-controlled, parallel trial consisting of a  
284 24-week treatment period. Patients could not be on more than 2 other anticonvulsants and  
285 valproate was not allowed. Patients were randomized to receive placebo, a target dose of  
286 300 mg/day of LAMICTAL, or a target dose of 500 mg/day of LAMICTAL. The median  
287 reductions in the frequency of all partial seizures relative to baseline were 8% in patients  
288 receiving placebo, 20% in patients receiving 300 mg/day of LAMICTAL, and 36% in patients  
289 receiving 500 mg/day of LAMICTAL. The seizure frequency reduction was statistically  
290 significant in the 500-mg/day group compared to the placebo group, but not in the 300-mg/day  
291 group.

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

298 The third study (n = 41) was a double-blind, placebo-controlled, crossover trial consisting of  
299 two 12-week treatment periods separated by a 4-week washout period. Patients could not be on  
300 more than 2 other anticonvulsants. Thirteen patients were on concomitant valproate; these  
301 patients received 150 mg/day of LAMICTAL. The 28 other patients had a target dose of  
302 300 mg/day of LAMICTAL. The median change in seizure frequency was a 26% reduction on  
303 LAMICTAL compared to placebo (p<0.01).

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

#### 306 ***Adjunctive Therapy With LAMICTAL in Pediatric Patients With Partial Seizures:***

307 The effectiveness of LAMICTAL as adjunctive therapy in pediatric patients with partial seizures  
308 was established in a multicenter, double-blind, placebo-controlled trial in 199 patients aged 2 to  
309 16 years (n = 98 on LAMICTAL, n = 101 on placebo). Following an 8-week baseline phase,  
310 patients were randomized to 18 weeks of treatment with LAMICTAL or placebo added to their  
311 current AED regimen of up to 2 drugs. Patients were dosed based on body weight and valproate  
312 use. Target doses were designed to approximate 5 mg/kg per day for patients taking valproate  
313 (maximum dose, 250 mg/day) and 15 mg/kg per day for the patients not taking valproate  
314 (maximum dose, 750 mg per day). The primary efficacy endpoint was percentage change from  
315 baseline in all partial seizures. For the intent-to-treat population, the median reduction of all  
316 partial seizures was 36% in patients treated with LAMICTAL and 7% on placebo, a difference  
317 that was statistically significant (p<0.01).

#### 318 ***Adjunctive Therapy With LAMICTAL in Pediatric and Adult Patients With***

319 **Lennox-Gastaut Syndrome:** The effectiveness of LAMICTAL as adjunctive therapy in  
320 patients with Lennox-Gastaut syndrome was established in a multicenter, double-blind,  
321 placebo-controlled trial in 169 patients aged 3 to 25 years (n = 79 on LAMICTAL, n = 90 on  
322 placebo). Following a 4-week single-blind, placebo phase, patients were randomized to 16 weeks  
323 of treatment with LAMICTAL or placebo added to their current AED regimen of up to 3 drugs.  
324 Patients were dosed on a fixed-dose regimen based on body weight and valproate use. Target  
325 doses were designed to approximate 5 mg/kg per day for patients taking valproate (maximum  
326 dose, 200 mg/day) and 15 mg/kg per day for patients not taking valproate (maximum dose,  
327 400 mg/day). The primary efficacy endpoint was percentage change from baseline in major  
328 motor seizures (atonic, tonic, major myoclonic, and tonic-clonic seizures). For the intent-to-treat  
329 population, the median reduction of major motor seizures was 32% in patients treated with  
330 LAMICTAL and 9% on placebo, a difference that was statistically significant (p<0.05). Drop  
331 attacks were significantly reduced by LAMICTAL (34%) compared to placebo (9%), as were  
332 tonic-clonic seizures (36% reduction versus 10% increase for LAMICTAL and placebo,  
333 respectively).

334 **Bipolar Disorder:** The effectiveness of LAMICTAL in the maintenance treatment of Bipolar I  
335 Disorder was established in 2 multicenter, double-blind, placebo-controlled studies in adult  
336 patients who met DSM-IV criteria for Bipolar I Disorder. Study 1 enrolled patients with a current  
337 or recent (within 60 days) depressive episode as defined by DSM-IV and Study 2 included  
338 patients with a current or recent (within 60 days) episode of mania or hypomania as defined by  
339 DSM-IV. Both studies included a cohort of patients (30% of 404 patients in Study 1 and 28% of  
340 171 patients in Study 2) with rapid cycling Bipolar Disorder (4 to 6 episodes per year).

341 In both studies, patients were titrated to a target dose of 200 mg of LAMICTAL, as add-on  
342 therapy or as monotherapy, with gradual withdrawal of any psychotropic medications during an  
343 8- to 16-week open-label period. Overall 81% of 1,305 patients participating in the open-label  
344 period were receiving 1 or more other psychotropic medications, including benzodiazepines,  
345 selective serotonin reuptake inhibitors (SSRIs), atypical antipsychotics (including olanzapine),  
346 valproate, or lithium, during titration of LAMICTAL. Patients with a CGI-severity score of 3 or  
347 less maintained for at least 4 continuous weeks, including at least the final week on monotherapy  
348 with LAMICTAL, were randomized to a placebo-controlled, double-blind treatment period for  
349 up to 18 months. The primary endpoint was TIME (time to intervention for a mood episode or  
350 one that was emerging, time to discontinuation for either an adverse event that was judged to be  
351 related to Bipolar Disorder or for lack of efficacy). The mood episode could be depression,  
352 mania, hypomania, or a mixed episode.

353 In Study 1, patients received double-blind monotherapy with LAMICTAL, 50 mg/day  
354 (n = 50), LAMICTAL 200 mg/day (n = 124), LAMICTAL 400 mg/day (n = 47), or placebo  
355 (n = 121). LAMICTAL (200- and 400-mg/day treatment groups combined) was superior to  
356 placebo in delaying the time to occurrence of a mood episode. Separate analyses of the 200 and  
357 400 mg/day dose groups revealed no added benefit from the higher dose.

358 In Study 2, patients received double-blind monotherapy with LAMICTAL (100 to  
359 400 mg/day, n = 59), or placebo (n = 70). LAMICTAL was superior to placebo in delaying the  
360 time to occurrence of a mood episode. The mean LAMICTAL dose was about 211 mg/day.

361 Although these studies were not designed to separately evaluate time to the occurrence of  
362 depression or mania, a combined analysis for the two studies revealed a statistically significant  
363 benefit for LAMICTAL over placebo in delaying the time to occurrence of both depression and  
364 mania, although the finding was more robust for depression.

365

## 366 **INDICATIONS AND USAGE**

### 367 **Epilepsy:**

368 **Adjunctive Use:** LAMICTAL is indicated as adjunctive therapy for partial seizures in adults  
369 and pediatric patients ( $\geq 2$  years of age).

370 LAMICTAL is also indicated as adjunctive therapy for the generalized seizures of  
371 Lennox-Gastaut syndrome in adult and pediatric patients ( $\geq 2$  years of age).

372 **Monotherapy Use:** LAMICTAL is indicated for conversion to monotherapy in adults with  
373 partial seizures who are receiving treatment with a single EIAED.

374 Safety and effectiveness of LAMICTAL have not been established (1) as initial monotherapy,  
375 (2) for conversion to monotherapy from non-enzyme-inducing AEDs (e.g., valproate), or (3) for  
376 simultaneous conversion to monotherapy from 2 or more concomitant AEDs (see DOSAGE  
377 AND ADMINISTRATION).

378 Safety and effectiveness in patients below the age of 16 other than those with partial seizures  
379 and the generalized seizures of Lennox-Gastaut syndrome have not been established (see BOX  
380 WARNING).

381 **Bipolar Disorder:** LAMICTAL is indicated for the maintenance treatment of Bipolar I  
382 Disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania,  
383 mixed episodes) in patients treated for acute mood episodes with standard therapy. The  
384 effectiveness of LAMICTAL in the acute treatment of mood episodes has not been established.

385 The effectiveness of LAMICTAL as maintenance treatment was established in  
386 2 placebo-controlled trials of 18 months' duration in patients with Bipolar I Disorder as defined  
387 by DSM-IV (see CLINICAL STUDIES, Bipolar Disorder). The physician who elects to use  
388 LAMICTAL for periods extending beyond 18 months should periodically re-evaluate the long-  
389 term usefulness of the drug for the individual patient.

390

## 391 **CONTRAINDICATIONS**

392 LAMICTAL is contraindicated in patients who have demonstrated hypersensitivity to the drug  
393 or its ingredients.

394

## 395 **WARNINGS**

396 **SEE BOX WARNING REGARDING THE RISK OF SERIOUS RASHES REQUIRING**  
397 **HOSPITALIZATION AND DISCONTINUATION OF LAMICTAL.**

398       **ALTHOUGH BENIGN RASHES ALSO OCCUR WITH LAMICTAL, IT IS NOT**  
399       **POSSIBLE TO PREDICT RELIABLY WHICH RASHES WILL PROVE TO BE**  
400       **SERIOUS OR LIFE THREATENING. ACCORDINGLY, LAMICTAL SHOULD**  
401       **ORDINARILY BE DISCONTINUED AT THE FIRST SIGN OF RASH, UNLESS THE**  
402       **RASH IS CLEARLY NOT DRUG RELATED. DISCONTINUATION OF TREATMENT**  
403       **MAY NOT PREVENT A RASH FROM BECOMING LIFE THREATENING OR**  
404       **PERMANENTLY DISABLING OR DISFIGURING.**

405       **Serious Rash: *Pediatric Population:*** The incidence of serious rash associated with  
406 hospitalization and discontinuation of LAMICTAL in a prospectively followed cohort of  
407 pediatric patients with epilepsy receiving adjunctive therapy was approximately 0.8% (16 of  
408 1,983). When 14 of these cases were reviewed by 3 expert dermatologists, there was considerable  
409 disagreement as to their proper classification. To illustrate, one dermatologist considered none of  
410 the cases to be Stevens-Johnson syndrome; another assigned 7 of the 14 to this diagnosis. There  
411 was one rash related death in this 1,983 patient cohort. Additionally, there have been rare cases  
412 of toxic epidermal necrolysis with and without permanent sequelae and/or death in US and  
413 foreign postmarketing experience. It bears emphasis, accordingly, that LAMICTAL is only  
414 approved for use in those patients below the age of 16 who have partial seizures or generalized  
415 seizures associated with the Lennox-Gastaut syndrome (see INDICATIONS).

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

420       ***Adult Population:*** Serious rash associated with hospitalization and discontinuation of  
421 LAMICTAL occurred in 0.3%(11 of 3,348) of adult patients who received LAMICTAL in  
422 premarketing clinical trials of epilepsy. In the bipolar and other mood disorders clinical trials, the  
423 rate of serious rash was 0.08% (1 of 1,233) of adult patients who received LAMICTAL as initial  
424 monotherapy and 0.13% (2 of 1,538) of adult patients who received LAMICTAL as adjunctive  
425 therapy. No fatalities occurred among these individuals. However, in worldwide postmarketing  
426 experience, rare cases of rash-related death have been reported, but their numbers are too few to  
427 permit a precise estimate of the rate.

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

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

437 Other examples of serious and potentially life-threatening rash that did not lead to  
438 hospitalization also occurred in premarketing development. Among these, 1 case was reported to  
439 be Stevens-Johnson–like.

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

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

451 **Acute Multiorgan Failure:** Multiorgan failure, which in some cases has been fatal or  
452 irreversible, has been observed in patients receiving LAMICTAL. Fatalities associated with  
453 multiorgan failure and various degrees of hepatic failure have been reported in 2 of 3,796 adult  
454 patients and 4 of 2,435 pediatric patients who received LAMICTAL in clinical trials. No such  
455 fatalities have been reported in bipolar patients in clinical trials. Rare fatalities from multiorgan  
456 failure have also been reported in compassionate plea and postmarketing use. The majority of  
457 these deaths occurred in association with other serious medical events, including status  
458 epilepticus and overwhelming sepsis, and hantavirus making it difficult to identify the initial  
459 cause.

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

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

470 **Withdrawal Seizures:** As with other AEDs, LAMICTAL should not be abruptly discontinued.  
471 In patients with epilepsy there is a possibility of increasing seizure frequency. In clinical trials in  
472 patients with Bipolar Disorder, 2 patients experienced seizures shortly after abrupt withdrawal of  
473 LAMICTAL. However, there were confounding factors that may have contributed to the  
474 occurrence of seizures in these bipolar patients. Unless safety concerns require a more rapid  
475 withdrawal, the dose of LAMICTAL should be tapered over a period of at least 2 weeks (see

476 DOSAGE AND ADMINISTRATION).

477

478 **PRECAUTIONS**

479 **Dermatological Events (see BOX WARNING, WARNINGS):** Serious rashes associated  
480 with hospitalization and discontinuation of LAMICTAL have been reported. Rare deaths have  
481 been reported, but their numbers are too few to permit a precise estimate of the rate. There are  
482 suggestions, yet to be proven, that the risk of rash may also be increased by (1) coadministration  
483 of LAMICTAL with valproate, (2) exceeding the recommended initial dose of LAMICTAL, or  
484 (3) exceeding the recommended dose escalation for LAMICTAL. However, cases have been  
485 reported in the absence of these factors.

486 In epilepsy clinical trials, approximately 10% of all patients exposed to LAMICTAL  
487 developed a rash. In the Bipolar Disorder clinical trials, 14% of patients exposed to LAMICTAL  
488 developed a rash. Rashes associated with LAMICTAL do not appear to have unique identifying  
489 features. Typically, rash occurs in the first 2 to 8 weeks following treatment initiation. However,  
490 isolated cases have been reported after prolonged treatment (e.g., 6 months). Accordingly,  
491 duration of therapy cannot be relied upon as a means to predict the potential risk heralded by the  
492 first appearance of a rash.

493 Although most rashes resolved even with continuation of treatment with LAMICTAL, it is not  
494 possible to predict reliably which rashes will prove to be serious or life threatening.

495 **ACCORDINGLY, LAMICTAL SHOULD ORDINARILY BE DISCONTINUED AT THE**  
496 **FIRST SIGN OF RASH, UNLESS THE RASH IS CLEARLY NOT DRUG RELATED.**  
497 **DISCONTINUATION OF TREATMENT MAY NOT PREVENT A RASH FROM**  
498 **BECOMING LIFE THREATENING OR PERMANENTLY DISABLING OR**  
499 **DISFIGURING.**

500 **Use in Patients With Epilepsy:**

501 **Sudden Unexplained Death in Epilepsy (SUDEP):** During the premarketing  
502 development of LAMICTAL, 20 sudden and unexplained deaths were recorded among a cohort  
503 of 4,700 patients with epilepsy (5,747 patient-years of exposure).

504 Some of these could represent seizure-related deaths in which the seizure was not observed,  
505 e.g., at night. This represents an incidence of 0.0035 deaths per patient-year. Although this rate  
506 exceeds that expected in a healthy population matched for age and sex, it is within the range of  
507 estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving  
508 LAMICTAL (ranging from 0.0005 for the general population of patients with epilepsy, to 0.004  
509 for a recently studied clinical trial population similar to that in the clinical development program  
510 for LAMICTAL, to 0.005 for patients with refractory epilepsy). Consequently, whether these  
511 figures are reassuring or suggest concern depends on the comparability of the populations  
512 reported upon to the cohort receiving LAMICTAL and the accuracy of the estimates provided.  
513 Probably most reassuring is the similarity of estimated SUDEP rates in patients receiving  
514 LAMICTAL and those receiving another antiepileptic drug that underwent clinical testing in a

515 similar population at about the same time. Importantly, that drug is chemically unrelated to  
516 LAMICTAL. This evidence suggests, although it certainly does not prove, that the high SUDEP  
517 rates reflect population rates, not a drug effect.

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

#### 524 **Use in Patients With Bipolar Disorder:**

525 **Acute Treatment of Mood Episodes:** Safety and effectiveness of LAMICTAL in the  
526 acute treatment of mood episodes has not been established.

527 **Suicide:** The possibility of a suicide attempt is inherent in Bipolar Disorder, and close  
528 supervision of high-risk patients should accompany drug therapy. Prescriptions for LAMICTAL  
529 should be written for the smallest quantity of tablets consistent with good patient management, in  
530 order to reduce the risk of overdose. Overdoses have been reported for LAMICTAL, some of  
531 which have been fatal (see OVERDOSAGE).

532 **Addition of LAMICTAL to a Multidrug Regimen That Includes Valproate (Dosage  
533 Reduction):** Because valproate reduces the clearance of lamotrigine, the dosage of lamotrigine  
534 in the presence of valproate is less than half of that required in its absence (see DOSAGE AND  
535 ADMINISTRATION).

536 **Use in Patients With Concomitant Illness:** Clinical experience with LAMICTAL in  
537 patients with concomitant illness is limited. Caution is advised when using LAMICTAL in  
538 patients with diseases or conditions that could affect metabolism or elimination of the drug, such  
539 as renal, hepatic, or cardiac functional impairment.

540 Hepatic metabolism to the glucuronide followed by renal excretion is the principal route of  
541 elimination of lamotrigine (see CLINICAL PHARMACOLOGY).

542 A study in individuals with severe chronic renal failure (mean creatinine  
543 clearance = 13 mL/min) not receiving other AEDs indicated that the elimination half-life of  
544 unchanged lamotrigine is prolonged relative to individuals with normal renal function. Until  
545 adequate numbers of patients with severe renal impairment have been evaluated during chronic  
546 treatment with LAMICTAL, it should be used with caution in these patients, generally using a  
547 reduced maintenance dose for patients with significant impairment.

548 Because there is no experience with the use of LAMICTAL in patients with impaired liver  
549 function, the use in such patients may be associated with as yet unrecognized risks.

550 **Binding in the Eye and Other Melanin-Containing Tissues:** Because lamotrigine binds  
551 to melanin, it could accumulate in melanin-rich tissues over time. This raises the possibility that  
552 lamotrigine may cause toxicity in these tissues after extended use. Although ophthalmological  
553 testing was performed in one controlled clinical trial, the testing was inadequate to exclude subtle

554 effects or injury occurring after long-term exposure. Moreover, the capacity of available tests to  
555 detect potentially adverse consequences, if any, of lamotrigine's binding to melanin is unknown.

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

558 **Information for Patients:** Prior to initiation of treatment with LAMICTAL, the patient should  
559 be instructed that a rash or other signs or symptoms of hypersensitivity (e.g., fever,  
560 lymphadenopathy) may herald a serious medical event and that the patient should report any such  
561 occurrence to a physician immediately. In addition, the patient should notify his or her physician  
562 if worsening of seizure control occurs.

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

568 Patients should be advised to notify their physicians if they become pregnant or intend to  
569 become pregnant during therapy. Patients should be advised to notify their physicians if they  
570 intend to breast-feed or are breast-feeding an infant.

571 Patients should be informed of the availability of a patient information leaflet, and they should  
572 be instructed to read the leaflet prior to taking LAMICTAL. See PATIENT INFORMATION at  
573 the end of this labeling for the text of the leaflet provided for patients.

574 **Laboratory Tests:** The value of monitoring plasma concentrations of LAMICTAL has not  
575 been established. Because of the possible pharmacokinetic interactions between LAMICTAL and  
576 other AEDs being taken concomitantly (see Table 3), monitoring of the plasma levels of  
577 LAMICTAL and concomitant AEDs may be indicated, particularly during dosage adjustments. In  
578 general, clinical judgment should be exercised regarding monitoring of plasma levels of  
579 LAMICTAL and other anti-seizure drugs and whether or not dosage adjustments are necessary.

#### 580 **Drug Interactions:**

581 ***Effects of Lamotrigine on the Pharmacokinetics of Other Drugs:*** (see Table 3).

582 ***LAMICTAL Added to Carbamazepine:*** LAMICTAL has no appreciable effect on  
583 steady-state carbamazepine plasma concentration. Limited clinical data suggest there is a higher  
584 incidence of dizziness, diplopia, ataxia, and blurred vision in patients receiving carbamazepine  
585 with LAMICTAL than in patients receiving other EIAEDs with LAMICTAL (see ADVERSE  
586 REACTIONS). The mechanism of this interaction is unclear. The effect of lamotrigine on plasma  
587 concentrations of carbamazepine-epoxide is unclear. In a small subset of patients (n = 7) studied  
588 in a placebo-controlled trial, lamotrigine had no effect on carbamazepine-epoxide plasma  
589 concentrations, but in a small, uncontrolled study (n = 9), carbamazepine-epoxide levels were  
590 seen to increase.

591 ***LAMICTAL Added to Valproate:*** When LAMICTAL was administered to 18 healthy  
592 volunteers receiving valproate in a pharmacokinetic study, the trough steady-state valproate

593 concentrations in plasma decreased by an average of 25% over a 3-week period, and then  
594 stabilized. However, adding LAMICTAL to the existing therapy did not cause a change in  
595 plasma valproate concentrations in either adult or pediatric patients in controlled clinical trials.

596 **LAMICTAL Added to Lithium:** The pharmacokinetics of lithium were not altered in  
597 healthy subjects (n = 20) by co-administration of 100 mg/day lamotrigine for 6 days.

598 **LAMICTAL Added to Phenytoin:** LAMICTAL has no appreciable effect on  
599 steady-state phenytoin plasma concentrations in patients with epilepsy.

600 Results of in vitro experiments suggest that lamotrigine does not reduce the clearance of drugs  
601 eliminated predominantly by CYP2D6 (see CLINICAL PHARMACOLOGY).

602 **Effects of Other Drugs on the Pharmacokinetics of Lamotrigine:** (see Table 3).

603 **Valproate Added to LAMICTAL:** The addition of valproate increases lamotrigine  
604 steady-state concentrations in normal volunteers by slightly more than 2-fold.

605 **Enzyme-Inducing Antiepileptic Drugs (e.g., carbamazepine, phenytoin,  
606 phenobarbital, primidone) Added to LAMICTAL:** The addition of EIAEDs decreases  
607 lamotrigine steady-state concentrations by approximately 40%.

608 **Bupropion Added to LAMICTAL:** The pharmacokinetics of a 100-mg single dose of  
609 lamotrigine in 12 healthy volunteers were not changed by co-administration of bupropion at  
610 300 mg/day starting 11 days before the lamotrigine dose.

611 **Other Psychotropic Drugs Added to LAMICTAL:** Results of in vitro experiments  
612 suggest that clearance of lamotrigine is unlikely to be reduced by concomitant administration of  
613 amitriptyline, clonazepam, clozapine, fluoxetine, haloperidol, lorazepam, phenelzine,  
614 risperidone, sertraline, or trazodone (see CLINICAL PHARMACOLOGY: Pharmacokinetics and  
615 Drug Metabolism).

616 **Interactions With Folate Inhibitors:** Lamotrigine is an inhibitor of dihydrofolate  
617 reductase. Prescribers should be aware of this action when prescribing other medications that  
618 inhibit folate metabolism.

619 The net effects of drug interactions with LAMICTAL are summarized in Table 3.

620

621 **Table 3. Summary of Drug Interactions With LAMICTAL**

Drug	Drug Plasma Concentration With Adjunctive LAMICTAL*	Lamotrigine Plasma Concentration With Adjunctive Drugs <sup>†</sup>
Phenytoin (PHT)	↔	↓
Carbamazepine (CBZ)	↔	↓
CBZ epoxide <sup>‡</sup>	?	
Valproate	↓	↑
Valproate + PHT and/or CBZ	Not assessed	↔
Lithium	↔	Not assessed
Bupropion	Not assessed	↔

622 \*From adjunctive clinical trials and volunteer studies.

623 <sup>†</sup>Net effects were estimated by comparing the mean clearance values obtained in adjunctive  
624 clinical trials and volunteers studies.625 <sup>‡</sup>Not administered, but an active metabolite of carbamazepine.

626 ↔ = No significant effect.

627 ? = Conflicting data.

628

629 **Drug/Laboratory Test Interactions:** None known.

630 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** No evidence of carcinogenicity  
631 was seen in 1 mouse study or 2 rat studies following oral administration of lamotrigine for up to  
632 2 years at maximum tolerated doses (30 mg/kg per day for mice and 10 to 15 mg/kg per day for  
633 rats, doses that are equivalent to 90 mg/m<sup>2</sup> and 60 to 90 mg/m<sup>2</sup>, respectively). Steady-state  
634 plasma concentrations ranged from 1 to 4 mcg/mL in the mouse study and 1 to 10 mcg/mL in the  
635 rat study. Plasma concentrations associated with the recommended human doses of 300 to  
636 500 mg/day are generally in the range of 2 to 5 mcg/mL, but concentrations as high as  
637 19 mcg/mL have been recorded.

638 Lamotrigine was not mutagenic in the presence or absence of metabolic activation when tested  
639 in 2 gene mutation assays (the Ames test and the in vitro mammalian mouse lymphoma assay). In  
640 2 cytogenetic assays (the in vitro human lymphocyte assay and the in vivo rat bone marrow  
641 assay), lamotrigine did not increase the incidence of structural or numerical chromosomal  
642 abnormalities.

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

646 **Pregnancy:** Pregnancy Category C. No evidence of teratogenicity was found in mice, rats, or  
647 rabbits when lamotrigine was orally administered to pregnant animals during the period of  
648 organogenesis at doses up to 1.2, 0.5, and 1.1 times, respectively, on a mg/m<sup>2</sup> basis, the highest

649 usual human maintenance dose (i.e., 500 mg/day). However, maternal toxicity and secondary  
650 fetal toxicity producing reduced fetal weight and/or delayed ossification were seen in mice and  
651 rats, but not in rabbits at these doses. Teratology studies were also conducted using bolus  
652 intravenous administration of the isethionate salt of lamotrigine in rats and rabbits. In rat dams  
653 administered an intravenous dose at 0.6 times the highest usual human maintenance dose, the  
654 incidence of intrauterine death without signs of teratogenicity was increased.

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

661 Lamotrigine did not affect fertility, teratogenesis, or postnatal development when rats were  
662 dosed prior to and during mating, and throughout gestation and lactation at doses equivalent to  
663 0.4 times the highest usual human maintenance dose on a mg/m<sup>2</sup> basis.

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

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

678 **Pregnancy Exposure Registry:** To facilitate monitoring fetal outcomes of pregnant women  
679 exposed to lamotrigine, physicians are encouraged to register patients, **before fetal outcome**  
680 **(e.g., ultrasound, results of amniocentesis, birth, etc.) is known**, and can obtain information  
681 by calling the Lamotrigine Pregnancy Registry at (800) 336-2176 (toll-free). Patients can enroll  
682 themselves in the North American Antiepileptic Drug Pregnancy Registry by calling (888) 233-  
683 2334 (toll free).

684 **Labor and Delivery:** The effect of LAMICTAL on labor and delivery in humans is unknown.

685 **Use in Nursing Mothers:** Preliminary data indicate that lamotrigine passes into human milk.  
686 Because the effects on the infant exposed to LAMICTAL by this route are unknown,  
687 breast-feeding while taking LAMICTAL is not recommended.

688 **Pediatric Use:** LAMICTAL is indicated as adjunctive therapy for partial seizures in patients  
689 above 2 years of age and for the generalized seizures of Lennox-Gastaut syndrome. Safety and  
690 effectiveness for other uses in patients with epilepsy below the age of 16 years have not been  
691 established (see BOX WARNING).

692 Safety and effectiveness in patients below the age of 18 years with Bipolar Disorder has not  
693 been established.

694 **Geriatric Use:** Clinical studies of LAMICTAL for epilepsy and in Bipolar Disorder did not  
695 include sufficient numbers of subjects aged 65 and over to determine whether they respond  
696 differently from younger subjects. In general, dose selection for an elderly patient should be  
697 cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of  
698 decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

699

## 700 **ADVERSE REACTIONS**

701 **SERIOUS RASH REQUIRING HOSPITALIZATION AND DISCONTINUATION OF**  
702 **LAMICTAL, INCLUDING STEVENS-JOHNSON SYNDROME AND TOXIC**  
703 **EPIDERMAL NECROLYSIS, HAVE OCCURRED IN ASSOCIATION WITH**  
704 **THERAPY WITH LAMICTAL. RARE DEATHS HAVE BEEN REPORTED, BUT**  
705 **THEIR NUMBERS ARE TOO FEW TO PERMIT A PRECISE ESTIMATE OF THE**  
706 **RATE (see BOX WARNING).**

### 707 **Epilepsy:**

708 ***Most Common Adverse Events in All Clinical Studies: Adjunctive Therapy in***  
709 ***Adults With Epilepsy:*** The most commonly observed ( $\geq 5\%$ ) adverse experiences seen in  
710 association with LAMICTAL during adjunctive therapy in adults and not seen at an equivalent  
711 frequency among placebo-treated patients were: dizziness, ataxia, somnolence, headache,  
712 diplopia, blurred vision, nausea, vomiting, and rash. Dizziness, diplopia, ataxia, blurred vision,  
713 nausea, and vomiting were dose related. Dizziness, diplopia, ataxia, and blurred vision occurred  
714 more commonly in patients receiving carbamazepine with LAMICTAL than in patients receiving  
715 other EIAEDs with LAMICTAL. Clinical data suggest a higher incidence of rash, including  
716 serious rash, in patients receiving concomitant valproate than in patients not receiving valproate  
717 (see WARNINGS).

718 Approximately 11% of the 3,378 adult patients who received LAMICTAL as adjunctive  
719 therapy in premarketing clinical trials discontinued treatment because of an adverse experience.  
720 The adverse events most commonly associated with discontinuation were rash (3.0%), dizziness  
721 (2.8%), and headache (2.5%).

722 In a dose response study in adults, the rate of discontinuation of LAMICTAL for dizziness,  
723 ataxia, diplopia, blurred vision, nausea, and vomiting was dose related.

724 ***Monotherapy in Adults With Epilepsy:*** The most commonly observed ( $\geq 5\%$ ) adverse  
725 experiences seen in association with the use of LAMICTAL during the monotherapy phase of the  
726 controlled trial in adults not seen at an equivalent rate in the control group were vomiting,

727 coordination abnormality, dyspepsia, nausea, dizziness, rhinitis, anxiety, insomnia, infection,  
728 pain, weight decrease, chest pain, and dysmenorrhea. The most commonly observed ( $\geq 5\%$ )  
729 adverse experiences associated with the use of LAMICTAL during the conversion to  
730 monotherapy (add-on) period, not seen at an equivalent frequency among low-dose  
731 valproate-treated patients, were dizziness, headache, nausea, asthenia, coordination abnormality,  
732 vomiting, rash, somnolence, diplopia, ataxia, accidental injury, tremor, blurred vision, insomnia,  
733 nystagmus, diarrhea, lymphadenopathy, pruritus, and sinusitis.

734 Approximately 10% of the 420 adult patients who received LAMICTAL as monotherapy in  
735 premarketing clinical trials discontinued treatment because of an adverse experience. The adverse  
736 events most commonly associated with discontinuation were rash (4.5%), headache (3.1%), and  
737 asthenia (2.4%).

738 **Adjunctive Therapy in Pediatric Patients With Epilepsy:** The most commonly  
739 observed ( $\geq 5\%$ ) adverse experiences seen in association with the use of LAMICTAL as  
740 adjunctive treatment in pediatric patients and not seen at an equivalent rate in the control group  
741 were infection, vomiting, rash, fever, somnolence, accidental injury, dizziness, diarrhea,  
742 abdominal pain, nausea, ataxia, tremor, asthenia, bronchitis, flu syndrome, and diplopia.

743 In 339 patients age 2 to 16 years, 4.2% of patients on LAMICTAL and 2.9% of patients on  
744 placebo discontinued due to adverse experiences. The most commonly reported adverse  
745 experiences that led to discontinuation were rash for patients treated with LAMICTAL and  
746 deterioration of seizure control for patients treated with placebo.

747 Approximately 11.5% of the 1,081 pediatric patients who received LAMICTAL as adjunctive  
748 therapy in premarketing clinical trials discontinued treatment because of an adverse experience.  
749 The adverse events most commonly associated with discontinuation were rash (4.4%), reaction  
750 aggravated (1.7%), and ataxia (0.6%).

751 **Incidence in Controlled Clinical Studies of Epilepsy:** The prescriber should be aware  
752 that the figures in Tables 4, 5, 6, and 7 cannot be used to predict the frequency of adverse  
753 experiences in the course of usual medical practice where patient characteristics and other factors  
754 may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot  
755 be directly compared with figures obtained from other clinical investigations involving different  
756 treatments, uses, or investigators. An inspection of these frequencies, however, does provide the  
757 prescriber with one basis to estimate the relative contribution of drug and nondrug factors to the  
758 adverse event incidences in the population studied.

759 **Incidence in Controlled Adjunctive Clinical Studies in Adults With Epilepsy:**  
760 Table 4 lists treatment-emergent signs and symptoms that occurred in at least 2% of adult  
761 patients with epilepsy treated with LAMICTAL in placebo-controlled trials and were numerically  
762 more common in the patients treated with LAMICTAL. In these studies, either LAMICTAL or  
763 placebo was added to the patient's current AED therapy. Adverse events were usually mild to  
764 moderate in intensity.

765 **Table 4. Treatment-Emergent Adverse Event Incidence in Placebo-Controlled**  
 766 **Adjunctive Trials in Adult Patients With Epilepsy\* (Events in at least 2% of patients**  
 767 **treated with LAMICTAL and numerically more frequent than in the placebo group.)**

Body System/ Adverse Experience†	Percent of Patients Receiving Adjunctive LAMICTAL (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
Reaction aggravated (seizure exacerbation)	2	1
Digestive		
Nausea	19	10
Vomiting	9	4
Diarrhea	6	4
Dyspepsia	5	2
Constipation	4	3
Tooth disorder	3	2
Anorexia	2	1
Musculoskeletal		
Arthralgia	2	0
Nervous		
Dizziness	38	13
Ataxia	22	6
Somnolence	14	7
Incoordination	6	2
Insomnia	6	2
Tremor	4	1
Depression	4	3
Anxiety	4	3
Convulsion	3	1
Irritability	3	2
Speech disorder	3	0

Concentration disturbance	2	1
Respiratory		
Rhinitis	14	9
Pharyngitis	10	9
Cough increased	8	6
Skin and appendages		
Rash	10	5
Pruritus	3	2
Special senses		
Diplopia	28	7
Blurred vision	16	5
Vision abnormality	3	1
Urogenital		
Female patients only	(n = 365)	(n = 207)
Dysmenorrhea	7	6
Vaginitis	4	1
Amenorrhea	2	1

768 \* Patients in these adjunctive studies were receiving 1 to 3 concomitant EIAEDs in addition  
 769 to LAMICTAL or placebo. Patients may have reported multiple adverse experiences during  
 770 the study or at discontinuation; thus, patients may be included in more than one category.

771 † Adverse experiences reported by at least 2% of patients treated with LAMICTAL are  
 772 included.

773

774 In a randomized, parallel study comparing placebo and 300 and 500 mg/day of LAMICTAL,  
 775 some of the more common drug-related adverse events were dose related (see Table 5).

776

777 **Table 5. Dose-Related Adverse Events From a Randomized, Placebo-Controlled Trial**  
 778 **in Adults With Epilepsy**

Adverse Experience	Percent of Patients Experiencing Adverse Experiences		
	Placebo (n = 73)	LAMICTAL 300 mg (n = 71)	LAMICTAL 500 mg (n = 72)
Ataxia	10	10	28*†
Blurred vision	10	11	25*†
Diplopia	8	24*	49*†
Dizziness	27	31	54*†
Nausea	11	18	25*
Vomiting	4	11	18*

779 \*Significantly greater than placebo group (p<0.05).

780 †Significantly greater than group receiving LAMICTAL 300 mg (p<0.05).

781

782 Other events that occurred in more than 1% of patients but equally or more frequently in the  
 783 placebo group included: asthenia, back pain, chest pain, flatulence, menstrual disorder, myalgia,  
 784 paresthesia, respiratory disorder, and urinary tract infection.

785 The overall adverse experience profile for LAMICTAL was similar between females and  
 786 males, and was independent of age. Because the largest non-Caucasian racial subgroup was only  
 787 6% of patients exposed to LAMICTAL in placebo-controlled trials, there are insufficient data to  
 788 support a statement regarding the distribution of adverse experience reports by race. Generally,  
 789 females receiving either adjunctive LAMICTAL or placebo were more likely to report adverse  
 790 experiences than males. The only adverse experience for which the reports on LAMICTAL were  
 791 greater than 10% more frequent in females than males (without a corresponding difference by  
 792 gender on placebo) was dizziness (difference = 16.5%). There was little difference between  
 793 females and males in the rates of discontinuation of LAMICTAL for individual adverse  
 794 experiences.

795 ***Incidence in a Controlled Monotherapy Trial in Adults With Partial Seizures:***

796 Table 6 lists treatment-emergent signs and symptoms that occurred in at least 5% of patients with  
 797 epilepsy treated with monotherapy with LAMICTAL in a double-blind trial following  
 798 discontinuation of either concomitant carbamazepine or phenytoin not seen at an equivalent  
 799 frequency in the control group.

800

801 **Table 6. Treatment-Emergent Adverse Event Incidence in Adults With Partial Seizures**  
 802 **in a Controlled Monotherapy Trial\* (Events in at least 5% of patients treated with**  
 803 **LAMICTAL and numerically more frequent than in the valproate group.)**

Body System/ Adverse Experience <sup>†</sup>	Percent of Patients Receiving LAMICTAL Monotherapy <sup>‡</sup> (n = 43)	Percent of Patients Receiving Low-Dose Valproate <sup>§</sup> Monotherapy (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
Nervous		
Coordination abnormality	7	0
Dizziness	7	0
Anxiety	5	0
Insomnia	5	2
Respiratory		
Rhinitis	7	2
Urogenital (female patients only)	(n = 21)	(n = 28)
Dysmenorrhea	5	0

804 \* Patients in these studies were converted to LAMICTAL or valproate monotherapy from  
 805 adjunctive therapy with carbamazepine or phenytoin. Patients may have reported multiple  
 806 adverse experiences during the study; thus, patients may be included in more than one  
 807 category.

808 <sup>†</sup> Adverse experiences reported by at least 5% of patients are included.

809 <sup>‡</sup> Up to 500 mg/day.

810 <sup>§</sup> 1,000 mg/day.

811

812 Adverse events that occurred with a frequency of less than 5% and greater than 2% of patients  
813 receiving LAMICTAL and numerically more frequent than placebo were:

814 **Body as a Whole:** Asthenia, fever.

815 **Digestive:** Anorexia, dry mouth, rectal hemorrhage, peptic ulcer.

816 **Metabolic and Nutritional:** Peripheral edema.

817 **Nervous System:** Amnesia, ataxia, depression, hypesthesia, libido increase, decreased  
818 reflexes, increased reflexes, nystagmus, irritability, suicidal ideation.

819 **Respiratory:** Epistaxis, bronchitis, dyspnea.

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

821 **Special Senses:** Vision abnormality.

822 **Incidence in Controlled Adjunctive Trials in Pediatric Patients With Epilepsy:**

823 Table 7 lists adverse events that occurred in at least 2% of 339 pediatric patients who received  
824 LAMICTAL up to 15 mg/kg per day or a maximum of 750 mg per day. Reported adverse events  
825 were classified using COSTART terminology.  
826

827 **Table 7. Treatment-Emergent Adverse Event Incidence in Placebo-Controlled**  
 828 **Adjunctive Trials in Pediatric Patients With Epilepsy (Events in at least 2% of patients**  
 829 **treated with LAMICTAL and numerically more frequent than in the placebo group.)**

Body System/ Adverse Experience	Percent of Patients Receiving LAMICTAL (n =168)	Percent of Patients Receiving Placebo (n =171)
Body as a whole		
Infection	20	17
Fever	15	14
Accidental injury	14	12
Abdominal pain	10	5
Asthenia	8	4
Flu syndrome	7	6
Pain	5	4
Facial edema	2	1
Photosensitivity	2	0
Cardiovascular		
Hemorrhage	2	1
Digestive		
Vomiting	20	16
Diarrhea	11	9
Nausea	10	2
Constipation	4	2
Dyspepsia	2	1
Tooth disorder	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
<b>Respiratory</b>		
Pharyngitis	14	11
Bronchitis	7	5
Increased cough	7	6
Sinusitis	2	1
Bronchospasm	2	1
<b>Skin</b>		
Rash	14	12
Eczema	2	1
Pruritus	2	1
<b>Special senses</b>		
Diplopia	5	1
Blurred vision	4	1
Ear disorder	2	1
Vision abnormality	2	0
<b>Urogenital</b>		
Male and female patients		
Urinary tract infection	3	0
Male patients only	n = 93	n = 92
Penis disorder	2	0

830

831

832

833

**Bipolar Disorder:** The most commonly observed ( $\geq 5\%$ ) adverse experiences seen in association with the use of LAMICTAL as monotherapy (100 to 400 mg/day) in Bipolar Disorder in the 2 double-blind, placebo-controlled trials of 18 months' duration, and numerically more

834 frequent than in placebo-treated patients are included in Table 8. Adverse events that occurred in  
835 at least 5% of patients and were numerically more common during the dose escalation phase of  
836 LAMICTAL in these trials (when patients may have been receiving concomitant medications)  
837 compared to the monotherapy phase were: headache (25%), rash (11%), dizziness (10%),  
838 diarrhea (8%), dream abnormality (6%), and pruritus (6%).

839 During the monotherapy phase of the double-blind, placebo-controlled trials of 18 months'  
840 duration, 13% of 227 patients who received LAMICTAL (100 to 400 mg/day), 16% of  
841 190 patients who received placebo, and 23% of 166 patients who received lithium discontinued  
842 therapy because of an adverse experience. The adverse events which most commonly led to  
843 discontinuation of LAMICTAL were rash (3%) and mania/hypomania/mixed mood adverse  
844 events (2%). Approximately 16% of 2,401 patients who received LAMICTAL (50 to  
845 500 mg/day) for Bipolar Disorder in premarketing trials discontinued therapy because of an  
846 adverse experience; most commonly due to rash (5%) and mania/hypomania/mixed mood  
847 adverse events (2%).

848 ***Incidence in Controlled Clinical Studies of LAMICTAL for the Maintenance***  
849 ***Treatment of Bipolar I Disorder:*** Table 8 lists treatment-emergent signs and symptoms that  
850 occurred in at least 5% of patients with Bipolar Disorder treated with LAMICTAL monotherapy  
851 (100 to 400 mg/day), following the discontinuation of other psychotropic drugs, in 2  
852 double-blind, placebo-controlled trials of 18 months' duration and were numerically more  
853 frequent than in the placebo group.

854

855 **Table 8. Treatment-Emergent Adverse Event Incidence in 2 Placebo-Controlled Trials**  
 856 **in Adults With Bipolar I Disorder\* (Events in at least 5% of patients treated with**  
 857 **LAMICTAL monotherapy and numerically more frequent than in the placebo group.)**

Body System/ Adverse Experience†	Percent of Patients Receiving LAMICTAL n = 227	Percent of Patients Receiving Placebo n = 190
<b>General</b>		
Back pain	8	6
Fatigue	8	5
Abdominal pain	6	3
<b>Digestive</b>		
Nausea	14	11
Constipation	5	2
Vomiting	5	2
<b>Nervous System</b>		
Insomnia	10	6
Somnolence	9	7
Xerostomia (dry mouth)	6	4
<b>Respiratory</b>		
Rhinitis	7	4
Exacerbation of cough	5	3
Pharyngitis	5	4
<b>Skin</b>		
Rash (non serious)‡	7	5

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

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

863 ‡ In the overall bipolar and other mood disorders clinical trials, the rate of serious rash was  
 864 0.08% (1 of 1,233) of adult patients who received LAMICTAL as initial monotherapy  
 865 and 0.13% (2 of 1,538) of adult patients who received LAMICTAL as adjunctive therapy  
 866 (see WARNINGS).

867

868 These adverse events were usually mild to moderate in intensity.

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

872 Adverse events that occurred with a frequency of less than 5% and greater than 1% of patients  
873 receiving LAMICTAL and numerically more frequent than placebo were:

874 **General:** Fever, neck pain.

875 **Cardiovascular:** Migraine.

876 **Digestive:** Flatulence.

877 **Metabolic and Nutritional:** Weight gain, edema.

878 **Musculoskeletal:** Arthralgia, myalgia.

879 **Nervous System:** Amnesia, depression, agitation, emotional lability, dyspraxia, abnormal  
880 thoughts, dream abnormality, hypoesthesia.

881 **Respiratory:** Sinusitis.

882 **Urogenital:** Urinary frequency.

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

889 **Mania/Hypomania/Mixed Episodes:** During the double-blind, placebo-controlled clinical  
890 trials in Bipolar I Disorder in which patients were converted to LAMICTAL monotherapy (100 to  
891 400 mg/day) from other psychotropic medications and followed for durations up to 18 months,  
892 the rate of manic or hypomanic or mixed mood episodes reported as adverse experiences was 5%  
893 for patients treated with LAMICTAL (n = 227), 4% for patients treated with lithium (n = 166),  
894 and 7% for patient treated with placebo (n = 190). In all bipolar controlled trials combined,  
895 adverse events of mania (including hypomania and mixed mood episodes) were reported in 5%  
896 of patients treated with LAMICTAL (n = 956), 3% of patients treated with lithium (n = 280), and  
897 4% of patients treated with placebo (n = 803).

898 The overall adverse event profile for LAMICTAL was similar between females and males,  
899 between elderly and nonelderly patients, and among racial groups.

900 **Other Adverse Events Observed During All Clinical Trials For Pediatric and Adult**  
901 **Patients With Epilepsy or Bipolar Disorder and Other Mood Disorders:** LAMICTAL  
902 has been administered to 6,694 individuals for whom complete adverse event data was captured  
903 during all clinical trials, only some of which were placebo controlled. During these trials, all  
904 adverse events were recorded by the clinical investigators using terminology of their own  
905 choosing. To provide a meaningful estimate of the proportion of individuals having adverse  
906 events, similar types of events were grouped into a smaller number of standardized categories  
907 using modified COSTART dictionary terminology. The frequencies presented represent the  
908 proportion of the 6,694 individuals exposed to LAMICTAL who experienced an event of the  
909 type cited on at least one occasion while receiving LAMICTAL. All reported events are included  
910 except those already listed in the previous tables or elsewhere in the labeling, those too general to  
911 be informative, and those not reasonably associated with the use of the drug.

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

916 **Body as a Whole: Infrequent:** Allergic reaction, chills, halitosis, and malaise. **Rare:**  
917 Abdomen enlarged, abscess, and suicide/suicide attempt.

918 **Cardiovascular System: Infrequent:** Flushing, hot flashes, hypertension, palpitations,  
919 postural hypotension, syncope, tachycardia, and vasodilation. **Rare:** Angina pectoris, atrial  
920 fibrillation, deep thrombophlebitis, ECG abnormality, and myocardial infarction.

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

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

929 **Endocrine System: Rare:** Goiter and hypothyroidism.

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

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

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

938 **Nervous System: Frequent:** Confusion and paresthesia. **Infrequent:** Akathisia, apathy,  
939 aphasia, CNS depression, depersonalization, dysarthria, dyskinesia, euphoria, hallucinations,  
940 hostility, hyperkinesia, hypertonia, libido decreased, memory decrease, mind racing, movement  
941 disorder, myoclonus, panic attack, paranoid reaction, personality disorder, psychosis, sleep  
942 disorder, stupor, and suicidal ideation. **Rare:** Cerebellar syndrome, cerebrovascular accident,  
943 cerebral sinus thrombosis, choreoathetosis, CNS stimulation, delirium, delusions, dysphoria,  
944 dystonia, extrapyramidal syndrome, faintness, grand mal convulsions, hemiplegia, hyperalgesia,  
945 hyperesthesia, hypokinesia, hypotonia, manic depression reaction, muscle spasm, neuralgia,  
946 neurosis, paralysis, and peripheral neuritis.

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

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

951 defect.

952 **Urogenital System: Infrequent:** Abnormal ejaculation, breast pain, hematuria, impotence,  
953 menorrhagia, polyuria, urinary incontinence, and urine abnormality. **Rare:** Acute kidney failure,  
954 anorgasmia, breast abscess, breast neoplasm, creatinine increase, cystitis, dysuria, epididymitis,  
955 female lactation, kidney failure, kidney pain, nocturia, urinary retention, urinary urgency, and  
956 vaginal moniliasis.

957 **Postmarketing and Other Experience:** In addition to the adverse experiences reported  
958 during clinical testing of LAMICTAL, the following adverse experiences have been reported in  
959 patients receiving marketed LAMICTAL and from worldwide noncontrolled investigational use.  
960 These adverse experiences have not been listed above, and data are insufficient to support an  
961 estimate of their incidence or to establish causation.

962 **Blood and Lymphatic:** Agranulocytosis, aplastic anemia, disseminated intravascular  
963 coagulation, hemolytic anemia, neutropenia, pancytopenia, red cell aplasia.

964 **Gastrointestinal:** Esophagitis.

965 **Hepatobiliary Tract and Pancreas:** Pancreatitis.

966 **Immunologic:** Lupus-like reaction, vasculitis.

967 **Lower Respiratory:** Apnea.

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

970 **Neurology:** Exacerbation of parkinsonian symptoms in patients with pre-existing  
971 Parkinson's disease, tics.

972 **Non-site Specific:** Hypersensitivity reaction, multiorgan failure, progressive  
973 immunosuppression.

974

## 975 **DRUG ABUSE AND DEPENDENCE**

976 The abuse and dependence potential of LAMICTAL have not been evaluated in human  
977 studies.

978

## 979 **OVERDOSAGE**

980 **Human Overdose Experience:** Overdoses involving quantities up to 15 g have been  
981 reported for LAMICTAL, some of which have been fatal. Overdose has resulted in ataxia,  
982 nystagmus, increased seizures, decreased level of consciousness, coma, and intraventricular  
983 conduction delay.

984 **Management of Overdose:** There are no specific antidotes for LAMICTAL. Following a  
985 suspected overdose, hospitalization of the patient is advised. General supportive care is indicated,  
986 including frequent monitoring of vital signs and close observation of the patient. If indicated,  
987 emesis should be induced or gastric lavage should be performed; usual precautions should be  
988 taken to protect the airway. It should be kept in mind that lamotrigine is rapidly absorbed (see  
989 CLINICAL PHARMACOLOGY). It is uncertain whether hemodialysis is an effective means of

990 removing lamotrigine from the blood. In 6 renal failure patients, about 20% of the amount of  
991 lamotrigine in the body was removed by hemodialysis during a 4-hour session. A Poison Control  
992 Center should be contacted for information on the management of overdosage of LAMICTAL.  
993

994

## 994 **DOSAGE AND ADMINISTRATION**

### 995 **Epilepsy:**

996 **Adjunctive Use:** LAMICTAL is indicated as adjunctive therapy for partial seizures in adults  
997 and pediatric patients ( $\geq 2$  years of age). LAMICTAL is also indicated as adjunctive therapy for  
998 the generalized seizures of Lennox-Gastaut syndrome in adult and pediatric patients ( $\geq 2$  years of  
999 age).

1000 **Monotherapy Use:** LAMICTAL is indicated for conversion to monotherapy in adults with  
1001 partial seizures who are receiving treatment with a single EIAED (e.g., carbamazepine,  
1002 phenytoin, phenobarbital, etc.).

1003 **Safety and effectiveness of LAMICTAL have not been established (1) as initial**  
1004 **monotherapy, (2) for conversion to monotherapy from non-enzyme-inducing AEDs (e.g.,**  
1005 **valproate), or (3) for simultaneous conversion to monotherapy from 2 or more concomitant**  
1006 **AEDs.**

1007 **Safety and effectiveness in pediatric patients below the age of 16 years other than those**  
1008 **with partial seizures and the generalized seizures of Lennox-Gastaut syndrome have not**  
1009 **been established (see BOX WARNING).**

1010 **Bipolar Disorder:** LAMICTAL is indicated for the maintenance treatment of Bipolar I  
1011 Disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania,  
1012 mixed episodes) in patients treated for acute mood episodes with standard therapy. The  
1013 effectiveness of LAMICTAL in the acute treatment of mood episodes has not been established.

1014 **General Dosing Considerations for Epilepsy and Bipolar Disorder Patients:** The  
1015 risk of nonserious rash is increased when the recommended initial dose and/or the rate of dose  
1016 escalation of LAMICTAL is exceeded. There are suggestions, yet to be proven, that the risk of  
1017 severe, potentially life-threatening rash may be increased by (1) coadministration of LAMICTAL  
1018 with valproate, (2) exceeding the recommended initial dose of LAMICTAL, or (3) exceeding the  
1019 recommended dose escalation for LAMICTAL. However, cases have been reported in the  
1020 absence of these factors (see BOX WARNING). Therefore, it is important that the dosing  
1021 recommendations be followed closely.

1022 **Patients With Renal Functional Impairment:** Initial doses of LAMICTAL should be  
1023 based on patients' AED regimen (see above); reduced maintenance doses may be effective for  
1024 patients with significant renal functional impairment (see CLINICAL PHARMACOLOGY). Few  
1025 patients with severe renal impairment have been evaluated during chronic treatment with  
1026 LAMICTAL. Because there is inadequate experience in this population, LAMICTAL should be  
1027 used with caution in these patients.

### 1028 **Epilepsy:**

1029 **Adjunctive Therapy With LAMICTAL for Epilepsy:** This section provides specific  
1030 dosing recommendations for patients 2 to 12 years of age and patients greater than 12 years of  
1031 age. Within each of these age-groups, specific dosing recommendations are provided depending  
1032 upon whether or not the patient is receiving valproate (Tables 9 and 10 for patients 2 to 12 years  
1033 of age, Tables 11 and 12 for patients greater than 12 years of age). In addition, the section  
1034 provides a discussion of dosing for those patients receiving concomitant AEDs that have not  
1035 been systematically evaluated in combination with LAMICTAL.

1036 For dosing guidelines for LAMICTAL below, enzyme-inducing antiepileptic drugs (EIAEDs)  
1037 include phenytoin, carbamazepine, phenobarbital, and primidone.

1038 **Patients 2 to 12 Years of Age:** Recommended dosing guidelines for LAMICTAL  
1039 added to an antiepileptic drug (AED) regimen containing valproate are summarized in Table 9.  
1040 Recommended dosing guidelines for LAMICTAL added to EIAEDs are summarized in Table 10.

1041 **LAMICTAL Added to Antiepileptic Drugs Other Than Enzyme-Inducing**  
1042 **Antiepileptic Drugs and Valproate:** The effect of AEDs other than EIAEDs and valproate  
1043 on the metabolism of LAMICTAL is not currently known. Therefore, no specific dosing  
1044 guidelines can be provided in that situation. Conservative starting doses and dose escalations (as  
1045 with concomitant valproate) would be prudent; maintenance dosing would be expected to fall  
1046 between the maintenance dose with valproate and the maintenance dose without valproate, but  
1047 with an EIAED.

1048 Note that the starting doses and dose escalations listed in Tables 9 and 10 are different than  
1049 those used in clinical trials; however, the maintenance doses are the same as in clinical trials.  
1050 Smaller starting doses and slower dose escalations than those used in clinical trials are  
1051 recommended because of the suggestions that the risk of rash may be decreased by smaller  
1052 starting doses and slower dose escalations. Therefore, maintenance doses will take longer to  
1053 reach in clinical practice than in clinical trials. It may take several weeks to months to achieve an  
1054 individualized maintenance dose. Maintenance doses in patients weighing less than 30 kg,  
1055 regardless of age or concomitant AED, may need to be increased as much as 50%, based on  
1056 clinical response.

1057 **The smallest available strength of LAMICTAL Chewable Dispersible Tablets is 2 mg,**  
1058 **and only whole tablets should be administered. If the calculated dose cannot be achieved**  
1059 **using whole tablets, the dose should be rounded down to the nearest whole tablet (see**  
1060 **HOW SUPPLIED and PATIENT INFORMATION for a description of the available sizes**  
1061 **of LAMICTAL Chewable Dispersible Tablets).**

1062

1063 **Table 9. LAMICTAL Added to an Antiepileptic Regimen Containing Valproate in**  
 1064 **Patients 2 to 12 Years of Age**

Weeks 1 and 2		0.15 mg/kg/day in 1 or 2 divided doses, rounded down to the nearest whole tablet. Only whole tablets should be used for dosing.	
Weeks 3 and 4		0.3 mg/kg/day in 1 or 2 divided doses, rounded down to the nearest whole tablet.	
Weight based dosing can be achieved by using the following guide:			
If the patient's weight is		Give this daily dose, using the most appropriate combination of LAMICTAL 2 mg and 5 mg tablets	
Greater than	And less than	Weeks 1 and 2	Weeks 3 and 4
6.7 kg	14 kg	2 mg every <i>other</i> day	2 mg every day
14.1 kg	27 kg	2 mg every day	4 mg every day
27.1 kg	34 kg	4 mg every day	8 mg every day
34.1 kg	40 kg	5 mg every day	10 mg every day
Usual maintenance dose: 1 to 5 mg/kg/day (maximum 200 mg/day in 1 or 2 divided doses). To achieve the usual maintenance dose, subsequent doses 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 usual maintenance dose in patients adding LAMICTAL to valproate alone ranges from 1 to 3 mg/kg/day. Maintenance doses in patients weighing less than 30 kg may need to be increased by as much as 50%, based on clinical response.			

1065

1066 **Table 10. LAMICTAL Added to Enzyme-Inducing Antiepileptic Drugs (Without**  
 1067 **Valproate) in Patients 2 to 12 Years of Age**

Weeks 1 and 2		0.6 mg/kg/day in 2 divided doses, rounded down to the nearest whole tablet.	
Weeks 3 and 4		1.2 mg/kg/day in 2 divided doses, rounded down to the nearest whole tablet.	
Usual maintenance dose: 5 to 15 mg/kg/day (maximum 400 mg/day in 2 divided doses). To achieve the usual maintenance dose, subsequent doses 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. Maintenance doses in patients weighing less than 30 kg may need to be increased by as much as 50%, based on clinical response.			

1068

1069

1070

**Patients Over 12 Years of Age:** Recommended dosing guidelines for LAMICTAL added to valproate are summarized in Table 11. Recommended dosing guidelines for

1071 LAMICTAL added to EIAEDs are summarized in Table 12.

1072 **LAMICTAL Added to Antiepileptic Drugs Other Than Enzyme-Inducing**  
 1073 **Antiepileptic Drugs and Valproate:** The effect of AEDs other than EIAEDs and valproate  
 1074 on the metabolism of LAMICTAL is not currently known. Therefore, no specific dosing  
 1075 guidelines can be provided in that situation. Conservative starting doses and dose escalations (as  
 1076 with concomitant valproate) would be prudent; maintenance dosing would be expected to fall  
 1077 between the maintenance dose with valproate and the maintenance dose without valproate, but  
 1078 with an EIAED.

1079

1080 **Table 11. LAMICTAL Added to an Antiepileptic Drug Regimen Containing Valproate in**  
 1081 **Patients Over 12 Years of Age**

Weeks 1 and 2	25 mg every <i>other</i> day
Weeks 3 and 4	25 mg every day
Usual maintenance dose: 100 to 400 mg/day (1 or 2 divided doses). To achieve maintenance, doses may be increased by 25 to 50 mg/day every 1 to 2 weeks. The usual maintenance dose in patients adding LAMICTAL to valproate alone ranges from 100 to 200 mg/day.	

1082

1083 **Table 12. LAMICTAL Added to Enzyme-Inducing Antiepileptic Drugs (Without**  
 1084 **Valproate) in Patients Over 12 Years of Age**

Weeks 1 and 2	50 mg/day
Weeks 3 and 4	100 mg/day in 2 divided doses
Usual maintenance dose: 300 to 500 mg/day (in 2 divided doses). To achieve maintenance, doses may be increased by 100 mg/day every 1 to 2 weeks.	

1085

1086 **Conversion From a Single Enzyme-Inducing Antiepileptic Drug to Monotherapy**  
 1087 **With LAMICTAL in Patients  $\geq 16$  Years of Age With Epilepsy:** The goal of the transition  
 1088 regimen is to effect the conversion to monotherapy with LAMICTAL under conditions that  
 1089 ensure adequate seizure control while mitigating the risk of serious rash associated with the rapid  
 1090 titration of LAMICTAL.

1091 The conversion regimen involves 2 steps. In the first, LAMICTAL is titrated to the targeted  
 1092 dose while maintaining the dose of the EIAED at a fixed level; in the second step, the EIAED is  
 1093 gradually withdrawn over a period of 4 weeks.

1094 The recommended maintenance dose of LAMICTAL as monotherapy is 500 mg/day given in  
 1095 2 divided doses.

1096 LAMICTAL should be added to an EIAED to achieve a dose of 500 mg/day according to the  
 1097 guidelines in Table 12 above. The regimen for the withdrawal of the concomitant EIAED is

1098 based on experience gained in the controlled monotherapy clinical trial. In that trial, the  
1099 concomitant EIAED was withdrawn by 20% decrements each week over a 4-week period.

1100 Because of an increased risk of rash, the recommended initial dose and subsequent dose  
1101 escalations of LAMICTAL should not be exceeded (see BOX WARNING).

1102 **Conversion from the Combination of LAMICTAL and Valproate to Monotherapy**  
1103 **With LAMICTAL in Patients  $\geq$  16 Years of Age With Epilepsy:** Discontinuing valproate  
1104 is known to shorten the half-life of lamotrigine. However, there is insufficient information to  
1105 provide dosing guidelines for this conversion. The safety and effectiveness of LAMICTAL has  
1106 not been established for the conversion to monotherapy from the 2 drug combination of  
1107 LAMICTAL and valproate in patients with epilepsy.

1108 **Usual Maintenance Dose for Epilepsy:** The usual maintenance doses identified in the  
1109 tables above are derived from dosing regimens employed in the placebo-controlled adjunctive  
1110 studies in which the efficacy of LAMICTAL was established. In patients receiving multidrug  
1111 regimens employing EIAEDs **without valproate**, maintenance doses of adjunctive LAMICTAL  
1112 as high as 700 mg/day have been used. In patients receiving **valproate alone**, maintenance doses  
1113 of adjunctive LAMICTAL as high as 200 mg/day have been used. The advantage of using doses  
1114 above those recommended in the tables above has not been established in controlled trials.

1115 **Discontinuation Strategy for Patients With Epilepsy:** For patients receiving  
1116 LAMICTAL in combination with other AEDs, a reevaluation of all AEDs in the regimen should  
1117 be considered if a change in seizure control or an appearance or worsening of adverse  
1118 experiences is observed.

1119 If a decision is made to discontinue therapy with LAMICTAL, a step-wise reduction of dose  
1120 over at least 2 weeks (approximately 50% per week) is recommended unless safety concerns  
1121 require a more rapid withdrawal (see PRECAUTIONS).

1122 *Discontinuing an EIAED should prolong the half-life of lamotrigine; discontinuing valproate*  
1123 *should shorten the half-life of lamotrigine.*

1124 **Target Plasma Levels for Patients With Epilepsy:** A therapeutic plasma concentration  
1125 range has not been established for lamotrigine. Dosing of LAMICTAL should be based on  
1126 therapeutic response.

1127 **Bipolar Disorder:** The goal of maintenance treatment with LAMICTAL is to delay the time to  
1128 occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated  
1129 for acute mood episodes with standard therapy. The target dose of LAMICTAL is 200 mg/day  
1130 (100 mg/day in combination with valproate and 400 mg/day in combination with carbamazepine  
1131 or other enzyme-inducing drugs). In the clinical trials, doses up to 400 mg/day as monotherapy  
1132 were evaluated, however, no additional benefit was seen at 400 mg/day compared to 200 mg/day  
1133 (see CLINICAL STUDIES: Bipolar Disorder). Accordingly, doses above 200 mg/day are not  
1134 recommended. Treatment with LAMICTAL is introduced, based on concurrent medications,  
1135 according to the regimen outlined in Table 13. If other psychotropic medications are withdrawn  
1136 following stabilization, the dose of LAMICTAL should be adjusted. For patients discontinuing  
1137 valproate, the dose of LAMICTAL should be doubled over a 2 week period in equal weekly

1138 increments (see Table 14). For patients discontinuing carbamazepine or other enzyme inducing  
 1139 agents, the dose of LAMICTAL should remain constant for the first week and then should be  
 1140 decreased by half over a 2 week period in equal weekly decrements (see Table 14). The dose of  
 1141 LAMICTAL may then be further adjusted to the target dose (200 mg) as clinically indicated.

1142 If other drugs are subsequently introduced, the dose of LAMICTAL may need to be  
 1143 adjusted. In particular, the introduction of valproate requires reduction in the dose of  
 1144 LAMICTAL (see CLINICAL PHARMACOLOGY: Drug Interactions).

1145 Because of an increased risk of rash, the recommended initial dose and subsequent dose  
 1146 escalations of LAMICTAL should not be exceeded (see BOX WARNING).

1147

1148 **Table 13. Escalation Regimen for LAMICTAL for Patients With Bipolar Disorder**

	For Patients Not Taking Carbamazepine (or Other Enzyme-Inducing Drugs) or Valproate	For Patients Taking Valproate	For Patients Taking Carbamazepine (or Other Enzyme-Inducing Drugs) and Not Taking Valproate
Weeks 1 and 2	25 mg daily	25 mg every other day	50 mg daily
Weeks 3 and 4	50 mg daily	25 mg daily	100 mg daily, in divided doses
Week 5	100 mg daily	50 mg daily	200 mg daily, in divided doses
Week 6	200 mg daily	100 mg daily	300 mg daily, in divided doses
Week 7	200 mg daily	100 mg daily	up to 400 mg daily, in divided doses

1149

1150 **Table 14. Adjustments to LAMICTAL Dosing for Patients With Bipolar Disorder**  
 1151 **Following Discontinuation of Psychotropic Medications**

	Discontinuation of Psychotropic Drugs excluding Valproate, Carbamazepine, or Other Enzyme-Inducing Drugs	After Discontinuation of Valproate	After Discontinuation of Carbamazepine or Other Enzyme-Inducing Drugs
		Current LAMICTAL dose (mg/day) 100	Current LAMICTAL dose (mg/day) 400
Week 1	Maintain current LAMICTAL dose	150	400
Week 2	Maintain current LAMICTAL dose	200	300
Week 3 onward	Maintain current LAMICTAL dose	200	200

1152

1153 There is no body of evidence available to answer the question of how long the patient should  
 1154 remain on LAMICTAL therapy. Systematic evaluation of the efficacy of LAMICTAL in patients  
 1155 with either depression or mania who responded to standard therapy during an acute 8 to 16 week  
 1156 treatment phase and were then randomized to LAMICTAL or placebo for up to 76 weeks of  
 1157 observation for affective relapse demonstrated a benefit of such maintenance treatment (see  
 1158 CLINICAL STUDIES: Bipolar Disorder). Nevertheless, patients should be periodically  
 1159 reassessed to determine the need for maintenance treatment.

1160 **Discontinuation Strategy in Bipolar Disorder:** As with other AEDs, LAMICTAL  
 1161 should not be abruptly discontinued. In the controlled clinical trials, there was no increase in the  
 1162 incidence, type, or severity of adverse experiences following abrupt termination of LAMICTAL.  
 1163 In clinical trials in patients with bipolar disorder, 2 patients experienced seizures shortly after  
 1164 abrupt withdrawal of LAMICTAL. However, there were confounding factors that may have  
 1165 contributed to the occurrence of seizures in these bipolar patients. Discontinuation of  
 1166 LAMICTAL should involve a step-wise reduction of dose over at least 2 weeks (approximately  
 1167 50% per week) unless safety concerns require a more rapid withdrawal.

1168 **Administration of LAMICTAL Chewable Dispersible Tablets:** LAMICTAL Chewable  
 1169 Dispersible Tablets may be swallowed whole, chewed, or dispersed in water or diluted fruit juice.  
 1170 If the tablets are chewed, consume a small amount of water or diluted fruit juice to aid in  
 1171 swallowing.

1172 To disperse LAMICTAL Chewable Dispersible Tablets, add the tablets to a small amount of  
 1173 liquid (1 teaspoon, or enough to cover the medication). Approximately 1 minute later, when the  
 1174 tablets are completely dispersed, swirl the solution and consume the entire quantity immediately.  
 1175 *No attempt should be made to administer partial quantities of the dispersed tablets.*

1176

1177 **HOW SUPPLIED**1178 **LAMICTAL Tablets, 25-mg**

1179 White, scored, shield-shaped tablets debossed with "LAMICTAL" and "25", bottles of 100  
1180 (NDC 0173-0633-02).

1181 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled**  
1182 **Room Temperature] in a dry place.**

1183 **LAMICTAL Tablets, 100-mg**

1184 Peach, scored, shield-shaped tablets debossed with "LAMICTAL" and "100", bottles of 100  
1185 (NDC 0173-0642-55).

1186 **LAMICTAL Tablets, 150-mg**

1187 Cream, scored, shield-shaped tablets debossed with "LAMICTAL" and "150", bottles of 60  
1188 (NDC 0173-0643-60).

1189 **LAMICTAL Tablets, 200-mg**

1190 Blue, scored, shield-shaped tablets debossed with "LAMICTAL" and "200", bottles of 60  
1191 (NDC 0173-0644-60).

1192 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled**  
1193 **Room Temperature] in a dry place and protect from light.**

1194

1195 **LAMICTAL Chewable Dispersible Tablets, 2-mg**

1196 White to off-white, round tablets debossed with "LTG" over "2", bottles of 30 (NDC 0173-  
1197 0699-00). ORDER DIRECTLY FROM GlaxoSmithKline 1-800-334-4153.

1198 **LAMICTAL Chewable Dispersible Tablets, 5-mg**

1199 White to off-white, caplet-shaped tablets debossed with "GX CL2", bottles of 100 (NDC  
1200 0173-0526-00).

1201 **LAMICTAL Chewable Dispersible Tablets, 25-mg**

1202 White, super elliptical-shaped tablets debossed with "GX CL5", bottles of 100 (NDC 0173-  
1203 0527-00).

1204 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled**  
1205 **Room Temperature] in a dry place.**

1206

1207 **LAMICTAL Starter Kit for Patients Taking Valproate**

1208 **25-mg, white, scored, shield-shaped tablets debossed with "LAMICTAL" and "25", blisterpack**  
1209 **of 35 tablets (NDC 0173-0633-10).**

1210 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled**  
1211 **Room Temperature] in a dry place.**

1212

1213 **LAMICTAL Starter Kit for Patients Taking Enzyme-Inducing Drugs and Not**  
1214 **Taking Valproate**

1215 **25-mg**, white, scored, shield-shaped tablets debossed with "LAMICTAL" and "25" and  
 1216 **100-mg**, peach, scored, shield-shaped tablets debossed with "LAMICTAL" and "100",  
 1217 blisterpack of 84, 25-mg tablets and 14, 100-mg tablets (NDC 0081-0594-01).

1218 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled**  
 1219 **Room Temperature] in a dry place and protect from light.**

1220  
 1221 **LAMICTAL Starter Kit for Patients Not Taking Enzyme-Inducing Drugs or**  
 1222 **Valproate [FOR USE IN BIPOLAR PATIENTS ONLY]**

1223 **25-mg**, white, scored, shield-shaped tablets debossed with "LAMICTAL" and "25" and  
 1224 **100-mg**, peach, scored, shield-shaped tablets debossed with "LAMICTAL" and "100",  
 1225 blisterpack of 42, 25-mg tablets and 7, 100-mg tablets (NDC 0173-0594-02).

1226 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled**  
 1227 **Room Temperature] in a dry place and protect from light.**

1228  
 1229 **PATIENT INFORMATION**

1230 The following wording is contained in a separate leaflet provided for patients.

1231  
 1232 **Information for the Patient**

1233  
 1234 **LAMICTAL<sup>®</sup> (lamotrigine) Tablets**

1235

 <b>25 mg, white</b> Imprinted with <b>LAMICTAL 25</b>	 <b>100 mg, peach</b> Imprinted with <b>LAMICTAL 100</b>	 <b>150 mg, cream</b> Imprinted with <b>LAMICTAL 150</b>	 <b>200 mg, blue</b> Imprinted with <b>LAMICTAL 200</b>
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1236  
 1237 **LAMICTAL<sup>®</sup> (lamotrigine) Chewable Dispersible Tablets**

1238

 <b>2 mg, white</b> Imprinted with <b>LTG 2</b>	 <b>5 mg, white</b> Imprinted with <b>GX CL2</b>	 <b>25 mg, white</b> Imprinted with <b>GX CL5</b>
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1239  
 1240 **NOTE: The pictures above show actual tablet shape and size and the wording describes the**  
 1241 **color and printing that is on each strength of LAMICTAL Tablets and Chewable**

1242 **Dispersible Tablets. Before taking your medicine, it is important to compare the tablets you**  
1243 **receive from your doctor or pharmacist with these pictures to make sure you have received**  
1244 **the correct medicine.**

1245  
1246 Please read this leaflet carefully before you take LAMICTAL and read the leaflet provided  
1247 with any refill, in case any information has changed. This leaflet provides a summary of the  
1248 information about your medicine. Please do not throw away this leaflet until you have finished  
1249 your medicine. This leaflet does not contain all the information about LAMICTAL and is not  
1250 meant to take the place of talking with your doctor. If you have any questions about LAMICTAL,  
1251 ask your doctor or pharmacist.

1252 **Information About Your Medicine:**

1253 The name of your medicine is LAMICTAL (lamotrigine). The decision to use LAMICTAL is  
1254 one that you and your doctor should make together. When taking lamotrigine, it is important to  
1255 follow your doctor's instructions.

1256

1257 ***1. The Purpose of Your Medicine:***

1258 ***For Patients With Epilepsy:*** LAMICTAL is intended to be used either alone or in  
1259 combination with other medicines to treat seizures in people aged 2 years or older.

1260 ***For Patients With Bipolar Disorder:*** LAMICTAL is used as maintenance treatment of  
1261 Bipolar I Disorder to delay the time to occurrence of mood episodes in people aged 18 years or  
1262 older treated for acute mood episodes with standard therapy.

1263 ***2. Who Should Not Take LAMICTAL:***

1264 You should not take LAMICTAL if you had an allergic reaction to it in the past.

1265 ***3. Side Effects to Watch for:***

- 1266 • Most people who take LAMICTAL tolerate it well. Common side effects with LAMICTAL  
1267 include dizziness, headache, blurred or double vision, lack of coordination, sleepiness,  
1268 nausea, vomiting, insomnia, and rash. LAMICTAL may cause other side effects not listed in  
1269 this leaflet. If you develop any side effects or symptoms you are concerned about or need  
1270 more information, call your doctor.
- 1271 • Although most patients who develop rash while receiving LAMICTAL have mild to  
1272 moderate symptoms, some individuals may develop a serious skin reaction that requires  
1273 hospitalization. Rarely, deaths have been reported. These serious skin reactions are most  
1274 likely to happen within the first 8 weeks of treatment with LAMICTAL. Serious skin  
1275 reactions occur more often in children than in adults.
- 1276 • Rashes may be more likely to occur if you: (1) take LAMICTAL in combination with  
1277 valproate [DEPAKENE® (valproic acid) or DEPAKOTE® (divalproex sodium)], (2) take a  
1278 higher starting dose of LAMICTAL than your doctor prescribed, or (3) increase your dose of  
1279 LAMICTAL faster than prescribed.
- 1280 • It is not possible to predict whether a mild rash will develop into a more serious reaction.

1281 **Therefore, if you experience a skin rash, hives, fever, swollen lymph glands, painful**  
1282 **sores in the mouth or around the eyes, or swelling of lips or tongue, tell a doctor**  
1283 **immediately, since these symptoms may be the first signs of a serious reaction. A doctor**  
1284 **should evaluate your condition and decide if you should continue taking LAMICTAL.**

1285 ***4. The Use of LAMICTAL During Pregnancy and Breast-feeding:***

1286 The effects of LAMICTAL during pregnancy are not known at this time. If you are pregnant  
1287 or are planning to become pregnant, talk to your doctor. Some LAMICTAL passes into breast  
1288 milk and the effects of this on infants are unknown. Therefore, if you are breast-feeding, you  
1289 should discuss this with your doctor to determine if you should continue to take LAMICTAL.

1290 ***5. How to Use LAMICTAL:***

- 1291 • It is important to take LAMICTAL exactly as instructed by your doctor. The dose of  
1292 LAMICTAL must be increased slowly. It may take several weeks or months before your final  
1293 dosage can be determined by your doctor, based on your response.
- 1294 • Do not increase your dose of LAMICTAL or take more frequent doses than those indicated  
1295 by your doctor.
- 1296 • If you miss a dose of LAMICTAL, do not double your next dose.
- 1297 • Do NOT stop taking LAMICTAL or any of your other medicines unless instructed by your  
1298 doctor.
- 1299 • Use caution before driving a car or operating complex, hazardous machinery until you know  
1300 if LAMICTAL affects your ability to perform these tasks.
- 1301 • If you have epilepsy, tell your doctor if your seizures get worse or if you have any new types  
1302 of seizures.
- 1303 • Always tell your doctor and pharmacist if you are taking or plan to take any other prescription  
1304 or over-the-counter medicines.

1305 ***6. How to Take LAMICTAL:***

1306 LAMICTAL Tablets should be swallowed whole. Chewing the tablets may leave a bitter taste.  
1307 LAMICTAL Chewable Dispersible Tablets may be swallowed whole, chewed, or mixed in  
1308 water or diluted fruit juice. If the tablets are chewed, consume a small amount of water or diluted  
1309 fruit juice to aid in swallowing.

1310 To disperse LAMICTAL Chewable Dispersible Tablets, add the tablets to a small amount of  
1311 liquid (1 teaspoon, or enough to cover the medication) in a glass or spoon. Approximately  
1312 1 minute later, when the tablets are completely dispersed, mix the solution and take the entire  
1313 amount immediately.

1314 ***7. Storing Your Medicine:***

1315 Store LAMICTAL at room temperature away from heat and light. Always keep your  
1316 medicines out of the reach of children.

1317 This medicine was prescribed for your use only to treat seizures or to treat Bipolar Disorder.  
1318 Do not give the drug to others.

1319 If your doctor decides to stop your treatment, do not keep any leftover medicine unless your

1320 doctor tells you to. Throw away your medicine as instructed.

1321



1322

1323 GlaxoSmithKline

1324

1325 Research Triangle Park, NC 27709

1326

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1328

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1330

1331 (Date of Issue)

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1332

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**PHARMACIST--DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT**

---

1333

1334

**Information for the Patient**

1335

1336

**LAMICTAL® (lamotrigine) Tablets**

1337

1338

 <b>25 mg, white</b> Imprinted with <b>LAMICTAL 25</b>	 <b>100 mg, peach</b> Imprinted with <b>LAMICTAL 100</b>	 <b>150 mg, cream</b> Imprinted with <b>LAMICTAL 150</b>	 <b>200 mg, blue</b> Imprinted with <b>LAMICTAL 200</b>
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1339

1340

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1341

 <b>2 mg, white</b> Imprinted with <b>LTG 2</b>	 <b>5 mg, white</b> Imprinted with <b>GX CL2</b>	 <b>25 mg, white</b> Imprinted with <b>GX CL5</b>
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1342

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1371 nausea, vomiting, insomnia, and rash. LAMICTAL may cause other side effects not listed in  
1372 this leaflet. If you develop any side effects or symptoms you are concerned about or need  
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1376 hospitalization. Rarely, deaths have been reported. These serious skin reactions are most  
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1378 reactions occur more often in children than in adults.
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1380 valproate [DEPAKENE<sup>®</sup> (valproic acid) or DEPAKOTE<sup>®</sup> (divalproex sodium)], (2) take a  
1381 higher starting dose of LAMICTAL than your doctor prescribed, or (3) increase your dose of  
1382 LAMICTAL faster than prescribed.
- 1383 • It is not possible to predict whether a mild rash will develop into a more serious reaction.

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- 1397 • Do not increase your dose of LAMICTAL or take more frequent doses than those indicated  
1398 by your doctor.
- 1399 • If you miss a dose of LAMICTAL, do not double your next dose.
- 1400 • Do NOT stop taking LAMICTAL or any of your other medicines unless instructed by your  
1401 doctor.
- 1402 • Use caution before driving a car or operating complex, hazardous machinery until you know  
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- 1404 • If you have epilepsy, tell your doctor if your seizures get worse or if you have any new types  
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- 1406 • Always tell your doctor and pharmacist if you are taking or plan to take any other prescription  
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1415 1 minute later, when the tablets are completely dispersed, mix the solution and take the entire  
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1417 ***7. Storing Your Medicine:***

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1420 This medicine was prescribed for your use only to treat seizures or to treat Bipolar Disorder.  
1421 Do not give the drug to others.

1422 If your doctor decides to stop your treatment, do not keep any leftover medicine unless your

1423 doctor tells you to. Throw away your medicine as instructed.

1424



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1426 GlaxoSmithKline

1427 Research Triangle Park, NC 27709

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1433 (Date of Issue)

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 20-241/S-016

NDA 20-764/S-009

SmithKline Beecham Corporation  
d/b/a GlaxoSmithKline  
Attention: Elizabeth A. McConnell, Pharm.D.  
Associate Director, Regulatory Affairs  
Five Moore Drive  
P.O. Box 13398  
Research Triangle Park, NC 27709

Dear Dr. McConnell:

Please refer to your supplemental new drug applications dated November 29, 2001, received December 10, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lamictal (lamotrigine) Tablets and Lamictal (lamotrigine) Chewable Dispersible Tablets.

We acknowledge receipt of your submissions dated July 11, 2003 and October 17, 2003.

Your submission of July 11, 2003 constituted a complete response to our October 10, 2002 action letter.

These supplemental new drug applications propose revisions to the Lamictal (lamotrigine) Tablets and Lamictal (lamotrigine) Chewable Dispersible Tablets labeling to remove the restriction for withdrawing adult patients receiving Lamictal and valproic acid alone to monotherapy with Lamictal and to provide guidelines for withdrawing valproic acid to achieve monotherapy with Lamictal.

We have completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement

NDA 20-241/S-016

NDA 20-764/S-009

Page 2

NDA 20-241/S-016 and NDA 20-764/S-009.” Approval of these submissions by FDA is not required before the labeling is used.

### **Pediatrics**

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for ages 0 years up to 1 month of age and deferring pediatric studies for ages 1 month to 16 years for this application.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA for Lamictal conversion to monotherapy in pediatric patients ages 1 month to 16 years who are receiving treatment with valproate.

Final Report Submission: January 2009

Submit final study reports to this NDA. For administrative purposes, all submissions related to this/these pediatric postmarketing study commitment(s) must be clearly designated “**Required Pediatric Study Commitments**”.

### **Promotional Materials**

In addition, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

### **Dear Healthcare Professional Letters**

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

NDA 20-241/S-016

NDA 20-764/S-009

Page 3

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Jacqueline H. Ware, Pharm.D., Senior Regulatory Project Manager, at (301) 594-2850.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.

Director

Division of Neuropharmacological Drug Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

Enclosure

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

-----  
Russell Katz  
1/14/04 02:46:22 PM

## Active Ingredient Search Results from "OB\_Rx" table for query on "lamotrigine."

App# No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
<u>020764</u>		Yes	LAMOTRIGINE	TABLET, CHEWABLE; ORAL	25MG	LAMICTAL CD	GLAXOSMITHKLINE
<u>020764</u>		No	LAMOTRIGINE	TABLET, CHEWABLE; ORAL	2MG	LAMICTAL CD	GLAXOSMITHKLINE
<u>020764</u>		No	LAMOTRIGINE	TABLET, CHEWABLE; ORAL	5MG	LAMICTAL CD	GLAXOSMITHKLINE
<u>020241</u>		No	LAMOTRIGINE	TABLET; ORAL	100MG	LAMICTAL	GLAXOSMITHKLINE
<u>020241</u>		No	LAMOTRIGINE	TABLET; ORAL	150MG	LAMICTAL	GLAXOSMITHKLINE
<u>020241</u>		No	LAMOTRIGINE	TABLET; ORAL	200MG	LAMICTAL	GLAXOSMITHKLINE
<u>020241</u>		Yes	LAMOTRIGINE	TABLET; ORAL	25MG	LAMICTAL	GLAXOSMITHKLINE

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FDA/Center for Drug Evaluation and Research

Office of Generic Drugs

Division of Labeling and Program Support

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Orange Book Data Updated Through March, 2005

Patent and Generic Drug Product Data Last Updated: May 19, 2005

Patent and Exclusivity Search Results from query on Appl No 020764 Product 001 in the OB\_Rx list.

**Patent Data**

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
<u>020764</u>	001	4602017	JUL 22,2008			<u>U-106</u>
<u>020764</u>	001	5698226	JAN 29,2012			

**Exclusivity Data**

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
<u>020764</u>	001	<u>ODE</u>	<b>AUG 24,2005</b>
<u>020764</u>	001	<u>I-387</u>	<b>JAN 17,2006</b>
<u>020764</u>	001	<u>I-404</u>	<b>JUN 20,2006</b>

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents submitted on FDA Form 3542 and listed after August 18, 2003 will have one to three patent codes indicating specific patent claims as submitted by the sponsor and are detailed in the above table.
3. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
4. \*PED and PED represent pediatric exclusivity. Patents with pediatric exclusivity granted after August 18, 2003 will be indicated with \*PED as was done prior to August 18, 2003. Patents with \*PED added after August 18, 2003 will not contain any information relative to the patent itself other than the \*PED extension. Information related specifically to the patent will be conveyed on the original patent only.

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**Exclusivity Codes**

This page defines the exclusivity codes.

**Code Definition**

I-387 ADJUNCTIVE THERAPY OF PARTIAL SEIZURES IN PEDIATRIC PATIENTS GREATER THAN OR EQUAL TO 2 YEARS OF AGE

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# GlaxoWellcome

## IMMEDIATE ATTENTION REQUIRED

### DISPENSING ERRORS ALERT

June 6, 2000

Dear Pharmacist:

Glaxo Wellcome Inc. has received reports of prescription dispensing errors involving **LAMICTAL®** (lamotrigine) Tablets and **LAMISIL®** (terbinafine hydrochloride) Tablets resulting in serious adverse events. The error reports involve dispensing Lamictal Tablets when Lamisil Tablets were prescribed and the reverse scenario.

Patients with epilepsy who do not receive their **antiepileptic drug LAMICTAL** due to a dispensing error would be inadequately treated and could experience serious consequences including status epilepticus. Conversely, patients erroneously receiving Lamictal instead of their **antifungal drug LAMISIL** would be unnecessarily subjected to a risk of potential side effects (including serious rash). This is especially true if patients receive an initial high dose of Lamictal (see Prescribing Information for Lamictal, DOSAGE AND ADMINISTRATION section).

**LAMICTAL** is an **antiepileptic** drug marketed as 25-, 100-, 150-, and 200-mg six-sided, shield-shaped tablets bearing "Lamictal" and the numeric representation of the strength (e.g., "Lamictal 150"). Lamictal Chewable Dispersible Tablets are 5-mg and 25-mg white tablets engraved with "GX CL2" and "GX CL5," respectively. To initiate therapy with Lamictal, the dose is titrated over a period of several weeks.

**LAMISIL** is an **antifungal** drug marketed as 250-mg circular, biconvex, bevelled tablets bearing "Lamisil" on one side and "250" on the other side. The recommended dosage for Lamisil is one 250-mg tablet daily for six or twelve weeks depending on the affected nail. Topical formulations of Lamisil are also available by prescription and over-the-counter.

Please be alert for both written and oral prescriptions for **LAMICTAL** and **LAMISIL**, and promptly share this letter with your pharmacy staff. Measures to avoid dispensing errors should be assessed (e.g., computer entry and filling of prescriptions, product shelving, patient counseling) and implemented as appropriate.

If you become aware of a prescription dispensing error involving these products, please contact the appropriate manufacturer (Glaxo Wellcome Inc.: 1-800-334-4135; Novartis Pharmaceuticals Corp.: 1-888-669-6682), the USP Medication Errors Reporting Program (1-800-233-7767) or the FDA MEDWATCH program by phone 1-800-FDA-1088, by FAX 1-800-FDA-0178, by modem 1-800-FDA-7737, or by mail:

MEDWATCH HF-2  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

For further information on Lamictal, please call 1-888-TALK-2-GW (1-888-825-5249).

Thank you.

Sincerely,



N. Scott Sykes, MD  
Vice President  
North American Product Surveillance

PLEASE CONSULT COMPLETE PRESCRIBING INFORMATION FOR LAMICTAL ENCLOSED.

**Glaxo Wellcome Inc.**

Five Moore Drive  
PO Box 13398  
Research Triangle Park, NC  
27709-3398

Telephone  
919 483 2100

**GlaxoWellcome**

**IMPORTANT  
DRUG  
WARNING**

**IMMEDIATE ATTENTION REQUIRED  
DISPENSING ERRORS ALERT**

July 2000

Dear Pharmacist:

Glaxo Wellcome Inc. has received reports of prescription dispensing errors involving **LAMICTAL®** (lamotrigine) Tablets and **LAMISIL®** (terbinafine hydrochloride) Tablets resulting in serious adverse events. The error reports involve dispensing Lamictal Tablets when Lamisil Tablets were prescribed and the reverse scenario.

Patients with epilepsy who do not receive their **antiepileptic drug LAMICTAL** due to a dispensing error would be inadequately treated and could experience serious consequences including status epilepticus. Conversely, patients erroneously receiving Lamictal instead of their **antifungal drug LAMISIL** would be unnecessarily subjected to a risk of potential side effects (including serious rash). This is especially true if patients receive an initial high dose of Lamictal (see Prescribing Information for Lamictal, DOSAGE AND ADMINISTRATION section).

**LAMICTAL** is an **antiepileptic drug** marketed as 25-, 100-, 150-, and 200-mg six-sided, shield-shaped tablets bearing "Lamictal" and the numeric representation of the strength (e.g., "Lamictal 150"). Lamictal Chewable Dispersible Tablets are 5-mg and 25-mg white tablets engraved with "GX CL2" and "GX CL5," respectively. To initiate therapy with Lamictal, the dose is titrated over a period of several weeks.

**LAMISIL** is an **antifungal drug** marketed as 250-mg circular, biconvex, bevelled tablets bearing "Lamisil" on one side and "250" on the other side. The recommended dosage for Lamisil is one 250-mg tablet daily for six or twelve weeks depending on the affected nail. Topical formulations of Lamisil are also available by prescription and over-the-counter.

Please be alert for both written and oral prescriptions for **LAMICTAL** and **LAMISIL**, and promptly share this letter with your pharmacy staff. Measures to avoid dispensing errors should be assessed (e.g., computer entry and filling of prescriptions, product shelving, patient counseling) and implemented as appropriate.

Clear communication when prescribing any drug product is an important measure in the effort to reduce the occurrence of dispensing errors. If you become aware of a prescription dispensing error involving **LAMICTAL**, please contact Glaxo Wellcome Inc. at 1-800-334-4153; the USP Medication Errors Reporting Program (1-800-233-7767) or the FDA MEDWATCH program by phone 1-800-FDA-1088, by FAX 1-800-FDA-0178, by Internet <http://www.fda.gov/medwatch> or [www.fda.gov/medwatch](http://www.fda.gov/medwatch), or by mail:

MEDWATCH HF-2  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

For further information on Lamictal, please call 1-888-TALK-2-GW (1-888-825-5249).

Thank you.

Sincerely,



R. Scott Sykes, MD  
Vice President  
North American Product Surveillance

PLEASE CONSULT COMPLETE PRESCRIBING INFORMATION FOR LAMICTAL ENCLOSED.

**Glaxo Wellcome Inc.**

Five Moore Drive  
PO Box 13398  
Research Triangle Park, NC  
27709-3398

Telephone  
919 483 2100

# GlaxoWellcome

**IMPORTANT  
DRUG  
WARNING**

## DISPENSING ERRORS ALERT

August 2000

Dear Health Professional:

Medication dispensing errors are a serious threat to quality health care and necessitate the combined efforts of prescribers, dispensers, manufacturers and patients to minimize their occurrence. Glaxo Wellcome Inc. has received reports of dispensing errors involving **LAMICTAL**® (lamotrigine) Tablets and other prescription drugs; most of these errors have been with the prescription medication **LAMISIL**® (terbinafine hydrochloride) Tablets, some of which have resulted in serious adverse events. Your assistance is requested in clearly communicating oral and written prescriptions for these two products to help avoid future dispensing errors. For example, you might consider, when appropriate, including the intended use on prescriptions for these products. Please alert patients for whom you are prescribing these medications that they should carefully check the medication they receive and promptly bring any questions or concerns to the attention of the pharmacist. Additional efforts to address this situation within pharmacies are under way.

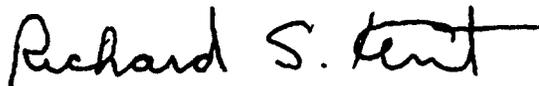
The error reports involve dispensing **LAMISIL** Tablets when **LAMICTAL** Tablets were prescribed and the reverse scenario. Patients erroneously receiving either medication would be unnecessarily subjected to the risk of adverse events. In addition, patients with epilepsy who do not receive their antiepileptic drug due to a dispensing error would be inadequately treated and could experience serious consequences including status epilepticus. Patients erroneously receiving **LAMICTAL** instead of their antifungal drug **LAMISIL** would not have the dose of **LAMICTAL** properly titrated and would be unnecessarily subjected to a risk of potential side effects, including serious rash (see enclosed Prescribing Information for **LAMICTAL** Tablets, Warning section and Dosage and Administration section).

**LAMICTAL** is an antiepileptic drug marketed as 25-mg (white), 100-mg (peach), 150-mg (cream), and 200-mg (blue), shield-shaped tablets bearing "Lamictal" and the numeric representation of the strength (e.g., "Lamictal 150"). Lamictal Chewable Dispersible Tablets are 5mg and 25mg white tablets engraved with "GX CL2" and "GX CL5," respectively. **LAMISIL** is an antifungal drug marketed as 250-mg circular tablets bearing "Lamisil" on one side and "250" on the other side.

Clear communication when prescribing any drug product is an important measure in the effort to reduce the occurrence of dispensing errors. If you become aware of a prescription dispensing error involving **LAMICTAL**, please contact Glaxo Wellcome Inc. at 1-800-334-4153; the USP Medication Errors Reporting Program (1-800-233-7767) or the FDA MEDWATCH program by phone 1-800-FDA-1088, by FAX 1-800-FDA-0178, by Internet <http://www.fda.gov/medwatch> or [www.fda.gov/medwatch](http://www.fda.gov/medwatch), or by mail:

MEDWATCH HF-2  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

Thank you.  
Sincerely,



Richard S. Kent, M.D.  
Vice President US Medical Operations

PLEASE CONSULT COMPLETE PRESCRIBING INFORMATION FOR LAMICTAL ENCLOSED.

**Glaxo Wellcome Inc.**

Five Moore Drive  
PO Box 13398  
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