CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-241/S-027 and 20-764/S-020

Trade Name: LAMICTAL

Generic Name: lamotrigine

Sponsor: GlaxoSmithKline

Approval Date: September 22, 2006

Indications: **Epilepsy**: Adjunctive Use: LAMICTAL is indicated as adjunctive therapy for partial seizures, the generalized seizures of Lennox-Gastaut syndrome, and primary generalized tonic-clonic seizures in adults and pediatric patients (2:2 years of age). **Monotherapy Use**: LAMICTAL is indicated for conversion to monotherapy in adults with partial seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single AED. **Bipolar Disorder**: LAMICTAL is indicated for the maintenance treatment of Bipolar I Disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy.

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APPLICATION NUMBER:

20-241/S-027 and 20-764/S-020

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APPLICATION NUMBER:

20-241/S-027 and 20-764/S-020

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-241/S-010/S-021/S-025/S-026/S-027
NDA 20-764/S-003/S-014/S-018/S-019/S-020

SmithKlineBeecham
d/b/a GlaxoSmithKline
Attn: Elizabeth McConnell, Pharm.D.
Associate Director, Regulatory Affairs, Neurology
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Dr. McConnell:

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act:

Name of Drug Product	Reference Number	Dated	Received	Provisions of supplement
Lamictal (lamotrigine) Tablets	NDA 20-241/S-027	Feb. 4, 2005	Feb. 7, 2005	Adjunctive treatment of primary generalized tonic-clonic seizures in adults and pediatric patients
Lamictal (lamotrigine) Chewable Dispersible Tablets	NDA 20-764/S-020	Feb. 4, 2005	Feb. 7, 2005	
Lamictal (lamotrigine) Tablets	NDA 20-241/S-010	Feb. 8, 1999	Feb. 9, 1999	Revisions to the **CLINICAL PHARMACOLOGY-Hepatic Disease** and corresponding subsections of **PRECAUTIONS-Use in Patients with Concomitant Illness** and **DOSAGE AND ADMINISTRATION Patients with Hepatic Impairment** to denote the results of a completed study evaluating the pharmacokinetics of lamotrigine in subjects with varying degrees of hepatic dysfunction. 2. Revisions to the "Hypersensitivity Reactions" and "Acute Multiorgan Failure" subsections of the **WARNINGS**
Lamictal (lamotrigine) Chewable Dispersible Tablets	NDA 20-764/S-003	Feb. 8, 1999	Feb. 9, 1999	

				section based on the October 2, 1998 conference call with the Agency regarding a spontaneous report of a patient whose hepatic dysfunction persisted despite discontinuation of lamotrigine. 3. Revisions to the **OVERDOSAGE-Human Overdose Experience** section based upon your review of spontaneous reports of overdose.
Lamictal (lamotrigine) Tablets	NDA 20-241/S-021	May 29, 2003	May 30, 2003	CBE: Revised wording under PRECAUTIONS: Dermatological Effects, DOSAGE AND ADMINISTRATION, Patient Information, and CLINICAL PHARMACOLOGY: Mechanism of Action
Lamictal (lamotrigine) Chewable Dispersible Tablets	NDA 20-764/S-014	May 29, 2003	May 30, 2003	
Lamictal (lamotrigine) Tablets	NDA 20-241/S-025	June 29, 2004	June 30, 2004	CBE: Revised wording under CLINICAL PHARMACOLOGY: Drug Interactions, PRECAUTIONS: Drug Interactions, and DOSAGE AND ADMINISTRATION
Lamictal (lamotrigine) Chewable Dispersible Tablets	NDA 20-764/S-018	June 29, 2004	June 30, 2004	
Lamictal (lamotrigine) Tablets	NDA 20-241/S-026	Aug. 20, 2004	Aug. 23, 2004	CBE: Revised Patient Information leaflet
Lamictal (lamotrigine) Chewable Dispersible Tablets	NDA 20-764/S-019	Aug. 20, 2004	Aug. 23, 2004	

We acknowledge receipt of your submissions dated February 19, 1999, October 6, 2000, August 11, 2004, May 27, 2005, April 11, 2005, August 31, 2005, and March 22, 2006.

Your submission of March 22, 2006 to the above supplements constituted a complete response to our October 3, 2002 and December 7, 2005 action letters. We acknowledge, as noted in your March 22, 2006 submission, that your response to the (b) (4) portion of the action letter is pending.

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 and text for the patient package insert).

Please submit an electronic version of the FPL 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 but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions **"FPL for approved supplements NDA 20-241/S-010/S-021/S-025/S-026/S-027** and **NDA 20-764/S-003/S-014/S-018/S-019/S-020."** Approval of these submissions by FDA is not required before the labeling is used.

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 note that you have fulfilled the pediatric study requirement for this application.

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 insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

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
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

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 Courtney Calder, PharmD, Regulatory Project Manager, at (301) 796-1050.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Division 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.

/s/

Russell Katz
9/22/2006 05:15:19 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-241/S-027 and 20-764/S-020

OTHER ACTION LETTER(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-241/S-021/S-025/S-026/S-027/(b) (4)
NDA 20-764/S-014/S-018/S-019/S-020/(b) (4)

SmithKlineBeecham
d/b/a GlaxoSmithKline
Attn: Elizabeth McConnell, Pharm.D.
Associate Director, Regulatory Affairs, Neurology
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Dr. McConnell:

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act:

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Lamictal (lamotrigine) Tablets	NDA 20-241/S-027	Feb. 4, 2005	Feb. 7, 2005	Adjunctive treatment of primary generalized tonic-clonic seizures in adults and pediatric patients
Lamictal (lamotrigine) Chewable Dispersible Tablets	NDA 20-764/S-020	Feb. 4, 2005	Feb. 7, 2005	
(b) (4)				
Lamictal (lamotrigine) Tablets	NDA 20-241/S-021	May 29, 2003	May 30, 2003	CBE: Revised wording under PRECAUTIONS: Dermatological Effects, DOSAGE AND ADMINISTRATION, Patient Information, and CLINICAL
Lamictal (lamotrigine) Chewable Dispersible Tablets	NDA 20-764/S-014	May 29, 2003	May 30, 2003	

				PHARMACOLOGY: Mechanism of Action
Lamictal (lamotrigine) Tablets	NDA 20-241/S-025	June 29, 2004	June 30, 2004	CBE: Revised wording under CLINICAL PHARMACOLOGY: Drug Interactions, PRECAUTIONS: Drug Interactions, and DOSAGE AND ADMINISTRATION
Lamictal (lamotrigine) Chewable Dispersible Tablets	NDA 20-764/S-018	June 29, 2004	June 30, 2004	
Lamictal (lamotrigine) Tablets	NDA 20-241/S-026	Aug. 20, 2004	Aug. 23, 2004	CBE: Revised Patient Information leaflet
(b) (4)				

We acknowledge receipt of your submissions dated August 11, 2004, May 27, 2005, April 11, 2005, and August 31, 2005.

We have reviewed these applications and they are approvable. Before they may be approved, you must address the following issues.

(b) (4)

(b) (4)

Oral Contraceptives (some of the following comments would also apply to the concomitant use of rifampin)

In your proposed labeling under DOSAGE AND ADMINISTRATION: Adjustments to the Maintenance Dose of Lamictal (1) Taking or Starting Oral Contraceptives, you suggest that patients being treated with Lamictal and concomitant oral contraceptives (OCs) who are not also taking

enzyme-inducing AEDs may need to be treated with a dose of Lamictal that is twice "…the recommended target maintenance dose…". However, this may give rise to clinical scenarios for which we have little to no experience. For example: 1) in patients being treated with a non-enzyme inducing AED, this could result in a daily dose of 750 mg; 2) in patients being treated with Lamictal monotherapy, this could result in a daily dose of 1000 mg; and 3) in the conversion to monotherapy regimen you propose, this could result in a daily dose of Lamictal of 1000 mg. Although we acknowledge the pharmacokinetic basis for your proposal, we have concerns about the tolerability of these doses. Indeed, in the conversion to monotherapy setting, you have not provided dosing recommendations to inform the prescriber how to lower a dose of Lamictal 1000 mg/day (or other doses between 1000 mg/day and 500 mg/day) to the recommended daily monotherapy dose of 500 mg. Further, during the "pill-free" week of the cycle, such large doses would be expected to result in dangerously high plasma levels of Lamictal. These issues will need to be adequately addressed before we can write adequate directions for the concomitant use of Lamictal and OCs.

In addition, assuming these issues can be resolved, we believe that the cyclical increase in plasma levels of Lamictal that occur during the latter part of the "pill-free" week (even at more modest doses than those discussed above) may also be associated with unacceptable adverse events in some patients. For this reason, we believe that this phenomenon must be described more prominently in product labeling than you have proposed. Accordingly, we have asked you, in the attached draft package insert, to draft an appropriate section to be placed as the first sub-section of the Precautions section.

Replacement of "Enzyme-Inducing AEDs" with the specific drug names.

You have proposed, in numerous sections of labeling, to replace the phrase "enzyme-inducing AEDs" with the specific list of such AEDs (as well as rifampin). Although we have no objection to this specific substitution in most sections of the label, we do have several concerns that we would like you to address.

We do not believe that this substitution is appropriate in those sections of labeling pertaining to dosing in patients with Bipolar Disorder. In these patients, we would not expect that most of the specific AEDs named are relevant. (b) (4)

(b) (4)

Removing the "enzyme-inducing" drugs language may be problematic in this regard.

Further, apropos our comments above related to the concomitant use of Lamictal and OCs, it might be reasonable to conclude that any drug with enzyme-inducing potency similar to that of the OCs should have the same dosing recommendations. However, as we have seen above, such recommendations may be problematic under certain circumstances.

Finally, we note that Lamictal is apparently inactivated via glucuronidation by the UDP-glucuronyl-transferase system. Presumably, then, drugs that induce Lamictal metabolism do so by inducing this enzyme system. However, we do not believe that the average prescriber would interpret the phrase "enzyme-inducing drug" as referring to an inducer of the UDP-glucuronyl-transferase system. More likely, in our view, prescribers would interpret this phrase as pertaining to the CYP450 enzyme system.

Therefore, you should consider explicitly referring to the specific system induced in product labeling when you draft labeling that uses the "enzyme-inducing drug" language.

(b) (4)

(b) (4)

Drug-Drug Interactions

We ask that you formally study the interaction of lamotrigine with tiagabine. You should also further address the potential for interaction between lamotrigine and gabapentin and between lamotrigine and pregabalin.

Labeling

As part of your response to this letter, we ask that you submit revised draft labeling for Lamictal. The attachment to this letter provides a draft of the labeling that the Agency asks you to adopt for Lamictal upon approval of this application. The base document used for our draft labeling is your approved label. Although sections of this proposal are taken verbatim from the labeling proposed by you in this application, other sections have been revised. Please also note that we have embedded throughout the text of the attached draft labeling several "Notes to Sponsor:" requesting further revisions of the labeling. Depending upon the results of the additional analyses we are requesting, labeling may need to be amended further.

We remind you of the December 3, 2002 approvable letter for CBE 20-241/S-010 and 20-764/S-003. In the attached label we have also addressed language from that letter.

We also ask that when you submit draft labeling for Lamictal, you include in the labeling all previous revisions, as reflected in the most recently approved package insert as well as any revisions you propose to the attached labeling. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes and identify which version of Lamictal labeling was used as the base document.

In addition, you must submit the content of labeling as described in 21 CFR 314.50(l)(5). This new submission requirement was published on December 11, 2003 (68 FR 69009) and was effective June 8, 2004. For additional information, consult the Guidance for Industry: *Regulatory Submissions in Electronic Format – Content of Labeling* (February 2004).

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

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 insert directly to:

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

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

If you have any questions, call Courtney R. Calder, Pharm.D., Regulatory Project Manager, at (301) 796-1050.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Division of Drug Evaluation I
Center for Drug Evaluation and Research

__62___ Page(s) Withheld

___ ___ Trade Secret / Confidential (b4)

___X___ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Russell Katz
12/7/2005 03:44:34 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-241/S-027 and 20-764/S-020

LABELING

PRESCRIBING INFORMATION

LAMICTAL®
(lamotrigine)
Tablets

LAMICTAL®
(lamotrigine)
Chewable Dispersible Tablets

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

OTHER THAN AGE, THERE ARE AS YET NO FACTORS IDENTIFIED THAT ARE KNOWN TO PREDICT THE RISK OF OCCURRENCE OR THE SEVERITY OF RASH ASSOCIATED WITH LAMICTAL. THERE ARE SUGGESTIONS, YET TO BE PROVEN, THAT THE RISK OF RASH MAY ALSO BE INCREASED BY (1) COADMINISTRATION OF LAMICTAL WITH VALPROATE (INCLUDES VALPROIC ACID AND DIVALPROEX SODIUM), (2) EXCEEDING THE RECOMMENDED INITIAL DOSE OF LAMICTAL, OR (3) EXCEEDING THE RECOMMENDED DOSE ESCALATION FOR LAMICTAL. HOWEVER, CASES HAVE BEEN REPORTED IN THE ABSENCE OF THESE FACTORS.

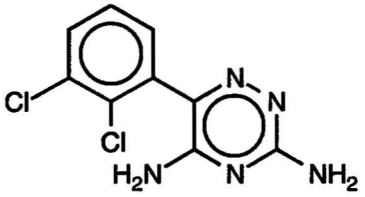
NEARLY ALL CASES OF LIFE-THREATENING RASHES ASSOCIATED WITH LAMICTAL HAVE OCCURRED WITHIN 2 TO 8 WEEKS OF TREATMENT INITIATION. HOWEVER, ISOLATED CASES HAVE BEEN REPORTED AFTER PROLONGED TREATMENT (E.G., 6 MONTHS). ACCORDINGLY, DURATION OF

THERAPY CANNOT BE RELIED UPON AS A MEANS TO PREDICT THE POTENTIAL RISK HERALDED BY THE FIRST APPEARANCE OF A RASH.

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

DESCRIPTION

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



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

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

CLINICAL PHARMACOLOGY

Mechanism of Action: The precise mechanism(s) by which lamotrigine exerts its anticonvulsant action are unknown. In animal models designed to detect anticonvulsant activity, lamotrigine was effective in preventing seizure spread in the maximum electroshock (MES) and pentylenetetrazol (scMet) tests, and prevented seizures in the visually and electrically evoked

after-discharge (EEAD) tests for antiepileptic activity. LAMICTAL also displayed inhibitory properties in the kindling model in rats both during kindling development and in the fully kindled state. The relevance of these models to human epilepsy, however, is not known.

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

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

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

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

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

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

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

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

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

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

Adult Study Population	Number of Subjects	T_{max}: Time of Maximum Plasma Concentration (h)	$t_{½}$: 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 carbamazepine, phenytoin, phenobarbital, or primidone† 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 carbamazepine, phenytoin, phenobarbital, or primidone†:				
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)

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

† Carbamazepine, phenobarbital, phenytoin, and primidone have been shown to increase the apparent clearance of lamotrigine. Estrogen-containing oral contraceptives and rifampin have also been shown to increase the apparent clearance of lamotrigine (see CLINICAL PHARMACOLOGY: Drug Interactions and PRECAUTIONS: Drug Interactions).

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

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

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

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

Drug Interactions: **The apparent clearance of lamotrigine is affected by the coadministration of certain medications.** Because lamotrigine is metabolized predominantly by glucuronic acid conjugation, drugs that induce or inhibit glucuronidation may affect the apparent clearance of lamotrigine.

Carbamazepine, phenytoin, phenobarbital, and primidone have been shown to increase the apparent clearance of lamotrigine (see DOSAGE AND ADMINISTRATION and

PRECAUTIONS: Drug Interactions). Most clinical experience is derived from patients taking these AEDs.

Estrogen-containing oral contraceptives and rifampin have also been shown to increase the apparent clearance of lamotrigine (see PRECAUTIONS: Drug Interactions).

Valproate decreases the apparent clearance of lamotrigine (i.e., more than doubles the elimination half-life of lamotrigine), whether given with or without carbamazepine, phenytoin, phenobarbital, or primidone. Accordingly, if lamotrigine is to be administered to a patient receiving valproate, lamotrigine must be given at a reduced dosage, of no more than half the dose used in patients not receiving valproate, even in the presence of drugs that increase the apparent clearance of lamotrigine (see DOSAGE AND ADMINISTRATION and PRECAUTIONS: Drug Interactions).

The following drugs were shown not to increase the apparent clearance of lamotrigine: felbamate, gabapentin, levetiracetam, oxcarbazepine, pregabalin, and topiramate. Zonisamide does not appear to change the pharmacokinetic profile of lamotrigine (see PRECAUTIONS: Drug Interactions).

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

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

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

Co-administration of olanzapine did not have a clinically relevant effect on LAMICTAL pharmacokinetics (see PRECAUTIONS: Drug Interactions).

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

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

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

and lamotrigine plasma concentrations at steady state following doses of 50 to 350 mg twice daily.

Elimination: (see Table 1).

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

Hepatic Disease: The pharmacokinetics of lamotrigine following a single 100-mg dose of LAMICTAL were evaluated in 24 subjects with mild, moderate, and severe hepatic dysfunction (Child-Pugh Classification system) and compared with 12 subjects without hepatic impairment. The patients with severe hepatic impairment were without ascites (n = 2) or with ascites (n = 5). The mean apparent clearance of lamotrigine in patients with mild (n = 12), moderate (n = 5), severe without ascites (n = 2), and severe with ascites (n = 5) liver impairment was 0.30 ± 0.09, 0.24 ± 0.1, 0.21 ± 0.04, and 0.15 ± 0.09 mL/min/kg, respectively, as compared to 0.37 ± 0.1 mL/min/kg in the healthy controls. Mean half-life of lamotrigine in patients with mild, moderate, severe without ascites, and severe with ascites liver impairment was 46 ± 20, 72 ± 44, 67 ± 11, and 100 ± 48 hours, respectively, as compared to 33 ± 7 hours in healthy controls (for dosing guidelines, see DOSAGE AND ADMINISTRATION: Patient With Hepatic Impairment).

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

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

Table 2. Mean Pharmacokinetic Parameters in Pediatric Patients With Epilepsy

Pediatric Study Population	Number of Subjects	T_{max} (h)	$t_{½}$ (h)	Cl/F (mL/min/kg)
Ages 10 months-5.3 years				
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone*	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 the apparent clearance of lamotrigine	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)
Ages 5-11 years				
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone*	7	1.6 (1.0-3.0)	7.0 (3.8-9.8)	2.54 (1.35-5.58)
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone* 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)
Ages 13-18 years				
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone*	11	‡	‡	1.3
Patients taking carbamazepine, phenytoin, phenobarbital, or primidone*plus valproate	8	‡	‡	0.5
Patients taking valproate only	4	‡	‡	0.3

*Carbamazepine, phenobarbital, phenytoin, and primidone have been shown to increase the apparent clearance of lamotrigine. Estrogen-containing oral contraceptives and rifampin have also been shown to increase the apparent clearance of lamotrigine (see CLINICAL PHARMACOLOGY: Drug Interactions and PRECAUTIONS: Drug Interactions).

†Two subjects were included in the calculation for mean T_{max}.

‡Parameter not estimated.

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

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

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

CLINICAL STUDIES

Epilepsy: The results of controlled clinical trials established the efficacy of LAMICTAL as monotherapy in adults with partial onset seizures already receiving treatment with carbamazepine, phenytoin, phenobarbital, or primidone as the single antiepileptic drug (AED), as adjunctive therapy in adults and pediatric patients age 2 to 16 with partial seizures, and as adjunctive therapy in the generalized seizures of Lennox-Gastaut syndrome in pediatric and adult patients.

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

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

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

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

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

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

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

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

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

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

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

Adjunctive Therapy With LAMICTAL in Pediatric and Adult Patients With Primary Generalized Tonic-Clonic Seizures: The effectiveness of LAMICTAL as adjunctive therapy in patients with primary generalized tonic-clonic seizures was established in a multicenter, double-blind, placebo-controlled trial in 117 pediatric and adult patients ≥ 2 years (n = 58 on LAMICTAL, n = 59 on placebo). Patients with at least 3 primary generalized tonic-clonic seizures during an 8-week baseline phase were randomized to 19 to 24 weeks of treatment with LAMICTAL or placebo added to their current AED regimen of up to 2 drugs. Patients were dosed on a fixed-dose regimen, with target doses ranging from 3 mg/kg/day to 12 mg/kg/day for pediatric patients and from 200 mg/day to 400 mg/day for adult patients based on concomitant AED.

The primary efficacy endpoint was percentage change from baseline in primary generalized tonic-clonic seizures. For the intent-to-treat population, the median percent reduction of primary

generalized tonic-clonic seizures was 66% in patients treated with LAMICTAL and 34% on placebo, a difference that was statistically significant (p=0.006).

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

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

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

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

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

INDICATIONS AND USAGE

Epilepsy:

Adjunctive Use: LAMICTAL is indicated as adjunctive therapy for partial seizures, the generalized seizures of Lennox-Gastaut syndrome, and primary generalized tonic-clonic seizures in adults and pediatric patients (≥2 years of age).

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

Safety and effectiveness of LAMICTAL have not been established (1) as initial monotherapy, (2) for conversion to monotherapy from AEDs other than carbamazepine, phenytoin, phenobarbital, primidone, or valproate, or (3) for simultaneous conversion to monotherapy from 2 or more concomitant AEDs (see DOSAGE AND ADMINISTRATION).

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

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

CONTRAINDICATIONS

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

WARNINGS

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

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

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

have been rare cases of toxic epidermal necrolysis with and without permanent sequelae and/or death in US and foreign postmarketing experience.

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

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

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

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

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

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

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

Acute Multiorgan Failure: Multiorgan failure, which in some cases has been fatal or irreversible, has been observed in patients receiving LAMICTAL. Fatalities associated with multiorgan failure and various degrees of hepatic failure have been reported in 2 of 3,796 adult

patients and 4 of 2,435 pediatric patients who received LAMICTAL in clinical trials. No such fatalities have been reported in bipolar patients in clinical trials. Rare fatalities from multiorgan failure have also been reported in compassionate plea and postmarketing use. The majority of these deaths occurred in association with other serious medical events, including status epilepticus and overwhelming sepsis, and hantavirus making it difficult to identify the initial cause.

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

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

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

PRECAUTIONS

Concomitant Use With Oral Contraceptives: Some estrogen-containing oral contraceptives have been shown to decrease serum concentrations of lamotrigine (see PRECAUTIONS: Drug Interactions). **Dosage adjustments will be necessary in most patients who start or stop estrogen-containing oral contraceptives while taking LAMICTAL (see DOSAGE AND ADMINISTRATION: Special Populations: Women and Oral Contraceptives: Adjustments to the Maintenance Dose of LAMICTAL).** During the week of inactive hormone preparation ("pill-free" week) of oral contraceptive therapy, plasma levels are expected to rise, as much as doubling by the end of the week. Adverse events consistent with elevated levels of lamotrigine, such as dizziness, ataxia, and diplopia, could occur.

Dermatological Events (see BOX WARNING, WARNINGS): Serious rashes associated with hospitalization and discontinuation of LAMICTAL have been reported. Rare deaths have been reported, but their numbers are too few to permit a precise estimate of the rate. There are suggestions, yet to be proven, that the risk of rash may also be increased by (1) coadministration of LAMICTAL with valproate, (2) exceeding the recommended initial dose of LAMICTAL, or

(3) exceeding the recommended dose escalation for LAMICTAL. However, cases have been reported in the absence of these factors.

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

Although most rashes resolved even with continuation of treatment with LAMICTAL, it is not possible to predict reliably which rashes will prove to be serious or life threatening. **ACCORDINGLY, LAMICTAL SHOULD ORDINARILY BE DISCONTINUED AT THE FIRST SIGN OF RASH, UNLESS THE RASH IS CLEARLY NOT DRUG RELATED. DISCONTINUATION OF TREATMENT MAY NOT PREVENT A RASH FROM BECOMING LIFE THREATENING OR PERMANENTLY DISABLING OR DISFIGURING.**

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

Use in Patients With Epilepsy:

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

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

LAMICTAL and those receiving another antiepileptic drug that underwent clinical testing in a similar population at about the same time. Importantly, that drug is chemically unrelated to LAMICTAL. This evidence suggests, although it certainly does not prove, that the high SUDEP rates reflect population rates, not a drug effect.

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

Use in Patients With Bipolar Disorder:

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

Children and Adolescents (less than 18 years of age): Treatment with antidepressants is associated with an increased risk of suicidal thinking and behavior in children and adolescents with major depressive disorder and other psychiatric disorders. It is not known whether LAMICTAL is associated with a similar risk in this population (see PRECAUTIONS: Clinical Worsening and Suicide Risk Associated With Bipolar Disorder).

Safety and effectiveness of LAMICTAL in patients below the age of 18 years with mood disorders have not been established.

Clinical Worsening and Suicide Risk Associated with Bipolar Disorder: Patients with bipolar disorder may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviors (suicidality) whether or not they are taking medications for bipolar disorder. Patients should be closely monitored for clinical worsening (including development of new symptoms) and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes.

In addition, patients with a history of suicidal behavior or thoughts, those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at an increased risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition (including development of new symptoms) and /or the emergence of suicidal ideation/behavior or thoughts of harming themselves and to seek medical advice immediately if these symptoms present.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who experience clinical worsening (including development of new symptoms) and/or the emergence of suicidal ideation/behavior especially if these symptoms are severe, abrupt in onset, or **were not part of the patient's presenting** symptoms.

Prescriptions for LAMICTAL should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Overdoses have been reported for LAMICTAL, some of which have been fatal (see OVERDOSAGE).

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

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

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

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

Because there is limited experience with the use of LAMICTAL in patients with impaired liver function, the use in such patients may be associated with as yet unrecognized risks (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Binding in the Eye and Other Melanin-Containing Tissues: Because lamotrigine binds to melanin, it could accumulate in melanin-rich tissues over time. This raises the possibility that lamotrigine may cause toxicity in these tissues after extended use. Although ophthalmological testing was performed in one controlled clinical trial, the testing was inadequate to exclude subtle effects or injury occurring after long-term exposure. Moreover, the capacity of available tests to detect potentially adverse consequences, if any, of lamotrigine's binding to melanin is unknown.

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

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

Patients should be advised that LAMICTAL may cause dizziness, somnolence, and other symptoms and signs of central nervous system (CNS) depression. Accordingly, they should be advised neither to drive a car nor to operate other complex machinery until they have gained

sufficient experience on LAMICTAL to gauge whether or not it adversely affects their mental and/or motor performance.

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

Women should be advised to notify their physician if they plan to start or stop use of oral contraceptives or other female hormonal preparations. Starting estrogen-containing oral contraceptives may significantly decrease lamotrigine plasma levels and stopping estrogen-containing oral contraceptives (including the **"pill-free" week) may significantly increase** lamotrigine plasma levels (see PRECAUTIONS: Drug Interactions). Women should also be advised to promptly notify their physician if they experience adverse events or changes in menstrual pattern (e.g., break-through bleeding) while receiving LAMICTAL in combination with these medications.

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

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

Laboratory Tests: The value of monitoring plasma concentrations of LAMICTAL has not been established. Because of the possible pharmacokinetic interactions between LAMICTAL and other drugs including AEDs (see Table 3), monitoring of the plasma levels of LAMICTAL and concomitant drugs may be indicated, particularly during dosage adjustments. In general, clinical judgment should be exercised regarding monitoring of plasma levels of LAMICTAL and other drugs and whether or not dosage adjustments are necessary.

Drug Interactions:

The net effects of drug interactions with LAMICTAL are summarized in Table 3 (see also DOSAGE AND ADMINISTRATION).

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

Gradual transient increases in lamotrigine plasma levels (approximate 2-fold increase) occurred during the week of i**nactive hormone preparation ("pill-free" week) for women not also** taking a drug that increased the clearance of lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). The increase in lamotrigine plasma levels will be greater

if the dose of LAMICTAL is increased in the few days before or during the "pill-free" week. Increases in lamotrigine plasma levels could result in dose-dependent adverse effects (see PRECAUTIONS: Concomitant Use With Oral Contraceptives).

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

The effects of doses of LAMICTAL other than 300 mg/day have not been studied in clinical trials.

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

Dosage adjustments will be necessary for most women receiving estrogen-containing oral contraceptive preparations (see DOSAGE AND ADMINISTRATION: Special Populations: Women and Oral Contraceptives).

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

Bupropion: The pharmacokinetics of a 100-mg single dose of LAMICTAL in healthy volunteers (n = 12) were not changed by co-administration of bupropion sustained-release formulation (150 mg twice a day) starting 11 days before LAMICTAL.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Other: Results of in vitro experiments suggest that clearance of lamotrigine is unlikely to be reduced by concomitant administration of amitriptyline, clonazepam, clozapine, fluoxetine, haloperidol, lorazepam, phenelzine, risperidone, sertraline, or trazodone (see CLINICAL PHARMACOLOGY: Pharmacokinetics and Drug Metabolism). Results of in vitro experiments suggest that lamotrigine does not reduce the clearance of drugs eliminated predominantly by CYP2D6 (see CLINICAL PHARMACOLOGY).

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Table 3. Summary of Drug Interactions With LAMICTAL

Drug	Drug Plasma Concentration With Adjunctive LAMICTAL*	Lamotrigine Plasma Concentration With Adjunctive Drugs†
Oral contraceptives (e.g., ethinylestradiol/levonorgestrel)‡	↔§	↓
Bupropion	Not assessed	↔
Carbamazepine (CBZ)	↔	↓
CBZ epoxide‖	?	
Felbamate	Not assessed	↔

Gabapentin	Not assessed	↔
Levetiracetam	↔	↔
Lithium	↔	Not assessed
Olanzapine	↔	↔[¶]
Oxcarbazepine	↔	↔
10-monohydroxy oxcarbazepine metabolite[#]	↔	
Phenobarbital/primidone	↔	↓
Phenytoin (PHT)	↔	↓
Pregabalin	↔	↔
Rifampin	Not assessed	↓
Topiramate	↔**	↔
Valproate	↓	↑
Valproate + PHT and/or CBZ	Not assessed	↔
Zonisamide	Not assessed	↔

* From adjunctive clinical trials and volunteer studies.

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

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

[§] Modest decrease in levonorgestrel (see PRECAUTIONS: Drug Interactions: Effect of LAMICTAL on Oral Contraceptives).

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

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

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

** Slight increase not expected to be clinically relevant.

↔ = No significant effect.

Drug/Laboratory Test Interactions: None known.

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

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

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

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

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

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

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

Although LAMICTAL was not found to be teratogenic in the above studies, lamotrigine decreases fetal folate concentrations in rats, an effect known to be associated with teratogenesis in animals and humans. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug

should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-Teratogenic Effects: As with other antiepileptic drugs, physiological changes during pregnancy may affect lamotrigine concentrations and/or therapeutic effect. There have been reports of decreased lamotrigine concentrations during pregnancy and restoration of pre-partum concentrations after delivery. Dosage adjustments may be necessary to maintain clinical response.

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

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

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

Pediatric Use: LAMICTAL is indicated as adjunctive therapy for partial seizures, for the generalized seizures of Lennox-Gastaut syndrome, and primary generalized tonic-clonic seizures in patients above 2 years of age. .

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

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

ADVERSE REACTIONS

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

Epilepsy:

Most Common Adverse Events in All Clinical Studies: Adjunctive Therapy in Adults With Epilepsy: The most commonly observed (≥5%) adverse experiences seen in association with LAMICTAL during adjunctive therapy in adults and not seen at an equivalent frequency among placebo-treated patients were: dizziness, ataxia, somnolence, headache,

diplopia, blurred vision, nausea, vomiting, and rash. Dizziness, diplopia, ataxia, blurred vision, nausea, and vomiting were dose related. Dizziness, diplopia, ataxia, and blurred vision occurred more commonly in patients receiving carbamazepine with LAMICTAL than in patients receiving other AEDs with LAMICTAL. Clinical data suggest a higher incidence of rash, including serious rash, in patients receiving concomitant valproate than in patients not receiving valproate (see WARNINGS).

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

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

Monotherapy in Adults With Epilepsy: The most commonly observed (≥5%) adverse experiences seen in association with the use of LAMICTAL during the monotherapy phase of the controlled trial in adults not seen at an equivalent rate in the control group were vomiting, coordination abnormality, dyspepsia, nausea, dizziness, rhinitis, anxiety, insomnia, infection, pain, weight decrease, chest pain, and dysmenorrhea. The most commonly observed (≥5%) adverse experiences associated with the use of LAMICTAL during the conversion to monotherapy (add-on) period, not seen at an equivalent frequency among low-dose valproate-treated patients, were dizziness, headache, nausea, asthenia, coordination abnormality, vomiting, rash, somnolence, diplopia, ataxia, accidental injury, tremor, blurred vision, insomnia, nystagmus, diarrhea, lymphadenopathy, pruritus, and sinusitis.

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

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

In 339 patients age 2 to 16 years with partial seizures or generalized seizures of Lennox-Gastaut syndrome, 4.2% of patients on LAMICTAL and 2.9% of patients on placebo discontinued due to adverse experiences. The most commonly reported adverse experiences that led to discontinuation were rash for patients treated with LAMICTAL and deterioration of seizure control for patients treated with placebo.

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

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

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

Table 4. Treatment-Emergent Adverse Event Incidence in Placebo-Controlled Adjunctive Trials in Adult Patients With Epilepsy* (Events in at least 2% of patients 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

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

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

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

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

	Percent of Patients Experiencing Adverse Experiences		
Adverse Experience	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*

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

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

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

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

Incidence in a Controlled Monotherapy Trial in Adults With Partial Seizures: Table 6 lists treatment-emergent signs and symptoms that occurred in at least 5% of patients with epilepsy treated with monotherapy with LAMICTAL in a double-blind trial following discontinuation of either concomitant carbamazepine or phenytoin not seen at an equivalent frequency in the control group.

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

Body System/ Adverse Experience†	Percent of Patients Receiving LAMICTAL Monotherapy‡ (n = 43)	Percent of Patients Receiving Low-Dose Valproate§ 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

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

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

‡ Up to 500 mg/day.

§ 1,000 mg/day.

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

Body as a Whole: Asthenia, fever.

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

Metabolic and Nutritional: Peripheral edema.

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

Respiratory: Epistaxis, bronchitis, dyspnea.

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

Special Senses: Vision abnormality.

Incidence in Controlled Adjunctive Trials in Pediatric Patients With Epilepsy: Table 7 lists adverse events that occurred in at least 2% of 339 pediatric patients with partial seizures or generalized seizures of Lennox-Gastaut syndrome, who received LAMICTAL up to 15 mg/kg per day or a maximum of 750 mg per day. Reported adverse events were classified using COSTART terminology.

Table 7. Treatment-Emergent Adverse Event Incidence in Placebo-Controlled Adjunctive Trials in Pediatric Patients With Epilepsy (Events in at least 2% of patients 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
Respiratory		
Pharyngitis	14	11
Bronchitis	7	5
Increased cough	7	6
Sinusitis	2	1
Bronchospasm	2	1
Skin		
Rash	14	12
Eczema	2	1
Pruritus	2	1
Special senses		
Diplopia	5	1
Blurred vision	4	1
Ear disorder	2	1

Visual abnormality	2	0
Urogenital		
Male and female patients		
Urinary tract infection	3	0
Male patients only	n = 93	n = 92
Penis disorder	2	0

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

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

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

Table 8. Treatment-Emergent Adverse Event Incidence in 2 Placebo-Controlled Trials in Adults With Bipolar I Disorder* (Events in at least 5% of patients treated with 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
General		
Back pain	8	6
Fatigue	8	5
Abdominal pain	6	3
Digestive		
Nausea	14	11
Constipation	5	2
Vomiting	5	2
Nervous System		
Insomnia	10	6
Somnolence	9	7
Xerostomia (dry mouth)	6	4
Respiratory		
Rhinitis	7	4
Exacerbation of cough	5	3
Pharyngitis	5	4
Skin		
Rash (nonserious)‡	7	5

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

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

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

These adverse events were usually mild to moderate in intensity.

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

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

General: Fever, neck pain.

Cardiovascular: Migraine.

Digestive: Flatulence.

Metabolic and Nutritional: Weight gain, edema.

Musculoskeletal: Arthralgia, myalgia.

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

Respiratory: Sinusitis.

Urogenital: Urinary frequency.

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

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

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

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

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* adverse events are defined as

those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1,000 patients; *rare* adverse events are those occurring in fewer than 1/1,000 patients.

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

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

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

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

Endocrine System: Rare: Goiter and hypothyroidism.

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

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

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

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

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

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

Urogenital System: Infrequent: Abnormal ejaculation, breast pain, hematuria, impotence, menorrhagia, polyuria, urinary incontinence, and urine abnormality. ***Rare:*** Acute kidney failure,

anorgasmia, breast abscess, breast neoplasm, creatinine increase, cystitis, dysuria, epididymitis, female lactation, kidney failure, kidney pain, nocturia, urinary retention, urinary urgency, and vaginal moniliasis.

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

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

Gastrointestinal: Esophagitis.

Hepatobiliary Tract and Pancreas: Pancreatitis.

Immunologic: Lupus-like reaction, vasculitis.

Lower Respiratory: Apnea.

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

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

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

DRUG ABUSE AND DEPENDENCE

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

OVERDOSAGE

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

Management of Overdose: There are no specific antidotes for LAMICTAL. Following a suspected overdose, hospitalization of the patient is advised. General supportive care is indicated, including frequent monitoring of vital signs and close observation of the patient. If indicated, emesis should be induced or gastric lavage should be performed; usual precautions should be taken to protect the airway. It should be kept in mind that lamotrigine is rapidly absorbed (see CLINICAL PHARMACOLOGY). It is uncertain whether hemodialysis is an effective means of removing lamotrigine from the blood. In 6 renal failure patients, about 20% of the amount of lamotrigine in the body was removed by hemodialysis during a 4-hour session. A Poison Control Center should be contacted for information on the management of overdosage of LAMICTAL.

DOSAGE AND ADMINISTRATION

Epilepsy:

Adjunctive Use: LAMICTAL is indicated as adjunctive therapy for partial seizures, the generalized seizures of Lennox-Gastaut syndrome, and primary generalized tonic-clonic seizures in adult and pediatric patients (≥2 years of age).

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

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

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

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

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

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

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

The half-life of LAMICTAL is affected by other concomitant medications (see CLINICAL PHARMACOLOGY: Pharmacokinetics and Drug Metabolism).

See also DOSAGE AND ADMINISTRATION: Special Populations.

Special Populations: Women and Oral Contraceptives: Starting LAMICTAL in Women Taking Oral Contraceptives: Although estrogen-containing oral contraceptives have been shown to increase the clearance of lamotrigine (see PRECAUTIONS: Drug Interactions), no adjustments to the recommended dose escalation guidelines for LAMICTAL should be necessary solely based on the use of estrogen-containing oral contraceptives. Therefore, dose escalation should follow the recommended guidelines for initiating adjunctive therapy with LAMICTAL based on the concomitant AED (see Table 11). See below for adjustments to maintenance doses of LAMICTAL in women taking estrogen-containing oral contraceptives.

Adjustments to the Maintenance Dose of LAMICTAL: (1) Taking Estrogen-Containing Oral Contraceptives: For women not taking carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, the maintenance dose of LAMICTAL will in most cases need to be increased, by as much as 2-fold over the recommended target maintenance dose, in order to maintain a consistent lamotrigine plasma level (see PRECAUTIONS: Drug Interactions). ***(2) Starting Estrogen-Containing Oral Contraceptives:*** In women taking a stable dose of LAMICTAL and not taking carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, the maintenance dose will in most cases need to be increased by as much as 2-fold, in order to maintain a consistent lamotrigine plasma level. The dose increases should begin at the same time that the oral contraceptive is introduced and continue, based on clinical response, no more rapidly than 50 to 100 mg/day every week. Dose increases should not exceed the recommended rate unless lamotrigine plasma levels or clinical response support larger increases (see Table 11, column 2). Gradual transient increases in lamotrigine plasma levels may occur during the week of inactive hormonal preparation **("pill-free" week), and these increases will be** greater if dose increases are made in the days before or during the week of inactive hormonal preparation. Increased lamotrigine plasma levels could result in additional adverse events, such as dizziness, ataxia, and diplopia (see PRECAUTIONS: Drug Interactions). If adverse events attributable to LAMICTAL consistently occur during the "pill-free" week, dose adjustments to the overall maintenance dose may be necessary. Dose adjustments limited to the "pill-free" week are not recommended. For women taking LAMICTAL in addition to carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, no adjustment should be necessary to the dose of LAMICTAL. ***(3) Stopping Estrogen-Containing Oral Contraceptives:*** For women not taking carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, the maintenance dose of LAMICTAL will in most cases need to be decreased by as much as 50%, in order to maintain a consistent lamotrigine plasma level. The decrease in dose of LAMICTAL should not exceed

25% of the total daily dose per week over a 2-week period, unless clinical response or lamotrigine plasma levels indicate otherwise (see PRECAUTIONS: Drug Interactions). For women taking LAMICTAL in addition to carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, no adjustment to the dose of LAMICTAL should be necessary.

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

Patients With Hepatic Impairment: Experience in patients with hepatic impairment is limited. Based on a clinical pharmacology study in 24 patients with mild, moderate, and severe liver dysfunction (see CLINICAL PHARMACOLOGY), the following general recommendations can be made. No dosage adjustment is needed in patients with mild liver impairment. Initial, escalation, and maintenance doses should generally be reduced by approximately 25% in patients with moderate and severe liver impairment without ascites and 50% in patients with severe liver impairment with ascites. Escalation and maintenance doses may be adjusted according to clinical response.

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

Epilepsy:

Adjunctive Therapy With LAMICTAL for Epilepsy: This section provides specific dosing recommendations for patients 2 to 12 years of age and patients greater than 12 years of age. Within each of these age-groups, specific dosing recommendations are provided depending upon concomitant AED (Table 9 for patients 2 to 12 years of age and Table 11 for patients greater than 12 years of age). A weight based dosing guide for pediatric patients on concomitant valproate is provided in Table 10.

Patients 2 to 12 Years of Age: Recommended dosing guidelines are summarized in Table 9.

Note that some of the starting doses and dose escalations listed in Table 9 are different than those used in clinical trials; however, the maintenance doses are the same as in clinical trials. Smaller starting doses and slower dose escalations than those used in clinical trials are recommended because of the suggestions that the risk of rash may be decreased by smaller starting doses and slower dose escalations. Therefore, maintenance doses will take longer to reach in clinical practice than in clinical trials. It may take several weeks to months to achieve an individualized maintenance dose. Maintenance doses in patients weighing less than 30 kg,

regardless of age or concomitant AED, may need to be increased as much as 50%, based on clinical response.

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

Table 9. Escalation Regimen for LAMICTAL in Patients 2 to 12 Years of Age With Epilepsy

	For Patients Taking Valproate (see Table 10 for weight-based dosing guide)	For Patients Taking AEDs Other Than Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate*	For Patients Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone* and Not Taking Valproate
Weeks 1 and 2	**0.15 mg/kg/day** in 1 or 2 divided doses, rounded down to the nearest whole tablet (see Table 10 for weight-based dosing guide).	**0.3 mg/kg/day** in 1 or 2 divided doses, rounded down to the nearest whole tablet.	**0.6 mg/kg/day** in 2 divided doses, rounded down to the nearest whole tablet.
Weeks 3 and 4	**0.3 mg/kg/day** in 1 or 2 divided doses, rounded down to the nearest whole tablet (see Table 10 for weight-based dosing guide).	**0.6 mg/kg/day** in 2 divided doses, rounded down to the nearest whole tablet.	**1.2 mg/kg/day** in 2 divided doses, rounded down to the nearest whole tablet.
Weeks 5 onwards to maintenance	The dose should be increased every 1 to 2 weeks as follows: calculate 0.3 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily dose.	The dose should be increased every 1 to 2 weeks as follows: calculate 0.6 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily dose	The dose should be increased every 1 to 2 weeks as follows: calculate 1.2 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily dose

Usual Maintenance Dose	**1 to 5 mg/kg/day** (maximum 200 mg/day in 1 or 2 divided doses). **1 to 3 mg/kg/day** with valproate alone	**4.5 to 7.5 mg/kg/day** (maximum 300 mg/day in 2 divided doses)	**5 to 15 mg/kg/day** (maximum 400 mg/day in 2 divided doses)
Maintenance dose in patients less than 30 kg	May need to be increased by as much as 50%, based on clinical response	May need to be increased by as much as 50%, based on clinical response	May need to be increased by as much as 50%, based on clinical response

Note: Only whole tablets should be used for dosing

* Rifampin and estrogen-containing oral contraceptives have also been shown to increase the apparent clearance of lamotrigine (see PRECAUTIONS: Drug Interactions).

Table 10. The Initial Weight-Based Dosing Guide for Patients 2 to 12 Years Taking Valproate (Weeks 1 to 4) With Epilepsy

		:	
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 *other* 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

Patients Over 12 Years of Age: Recommended dosing guidelines are summarized in Table 11.

Table 11. Escalation Regimen for LAMICTAL in Patients Over 12 Years of Age With Epilepsy

	For Patients Taking Valproate	For Patients Taking AEDs Other Than Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate*	For Patients Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone* and Not Taking Valproate
Weeks 1 and 2	**25 mg every *other* day**	**25 mg every day**	**50 mg/day**
Weeks 3 and 4	**25 mg every day**	**50 mg/day**	**100 mg/day** (in 2 divided doses)
Weeks 5 onwards to maintenance	Increase by 25 to 50 mg/day every 1 to 2 weeks	Increase by 50 mg/day every 1 to 2 weeks	Increase by 100 mg/day every 1 to 2 weeks.
Usual Maintenance Dose	**100 to 400 mg/day** (1 or 2 divided doses) **100 to 200 mg/day with valproate alone**	**225 to 375 mg/day** (in 2 divided doses).	**300 to 500 mg/day** (in 2 divided doses).

* Rifampin and estrogen-containing oral contraceptives have also been shown to increase the apparent clearance of lamotrigine (see PRECAUTIONS: Drug Interactions).

Conversion From Adjunctive Therapy With Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate as the Single AED to Monotherapy With LAMICTAL in Patients ≥16 Years of Age With Epilepsy: The goal of the transition regimen is to effect the conversion to monotherapy with LAMICTAL under conditions that ensure adequate seizure control while mitigating the risk of serious rash associated with the rapid titration of LAMICTAL.

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

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

Conversion From Adjunctive Therapy With Carbamazepine, Phenytoin, Phenobarbital, or Primidone to Monotherapy With LAMICTAL: After achieving a dose of 500 mg/day of LAMICTAL according to Table 11, the concomitant AED should be withdrawn by 20% decrements each week over a 4-week period. The regimen for the withdrawal of the concomitant AED is based on experience gained in the controlled monotherapy clinical trial.

Conversion from Adjunctive Therapy With Valproate to Monotherapy With LAMICTAL: The conversion regimen involves 4 steps (see Table 12).

Table 12. Conversion From Adjunctive Therapy With Valproate to Monotherapy With LAMICTAL in Patients ≥16 Years of Age With Epilepsy

	LAMICTAL	Valproate
Step 1	Achieve a dose of 200 mg/day according to guidelines in Table 11 (if not already on 200 mg/day).	Maintain previous stable dose.
Step 2	Maintain at 200 mg/day.	Decrease to 500 mg/day by decrements no greater than 500 mg/day per week and then maintain the dose of 500 mg/day for 1 week.
Step 3	Increase to 300 mg/day and maintain for 1 week.	Simultaneously decrease to 250 mg/day and maintain for 1 week.
Step 4	Increase by 100 mg/day every week to achieve maintenance dose of 500 mg/day.	Discontinue.

Conversion from Adjunctive Therapy With Antiepileptic Drugs Other Than Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate to Monotherapy With LAMICTAL: No specific dosing guidelines can be provided for conversion to monotherapy with LAMICTAL with AEDs other than carbamazepine, phenobarbital, phenytoin, primidone, or valproate.

Usual Maintenance Dose for Epilepsy: The usual maintenance doses identified in Tables 9-11 are derived from dosing regimens employed in the placebo-controlled adjunctive studies in which the efficacy of LAMICTAL was established. In patients receiving multidrug regimens employing carbamazepine, phenytoin, phenobarbital, or primidone **without valproate**, maintenance doses of adjunctive LAMICTAL as high as 700 mg/day have been used. In patients receiving **valproate alone**, maintenance doses of adjunctive LAMICTAL as high as 200 mg/day have been used. The advantage of using doses above those recommended in Tables 9-12 has not been established in controlled trials.

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

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

Discontinuing carbamazepine, phenytoin, phenobarbital, or primidone should prolong the half-life of lamotrigine; discontinuing valproate should shorten the half-life of lamotrigine.

Bipolar Disorder: The goal of maintenance treatment with LAMICTAL is to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy. The target dose of LAMICTAL is 200 mg/day (100 mg/day in patients taking valproate,which decreases the apparent clearance of lamotrigine, and 400 mg/day in patients not taking valproate and taking either Carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, which increase the apparent clearance of lamotrigine). In the clinical trials, doses up to 400 mg/day as monotherapy were evaluated, however, no additional benefit was seen at 400 mg/day compared to 200 mg/day (see CLINICAL STUDIES: Bipolar Disorder). Accordingly, doses above 200 mg/day are not recommended. Treatment with LAMICTAL is introduced, based on concurrent medications, according to the regimen outlined in Table 13. If other psychotropic medications are withdrawn following stabilization, the dose of LAMICTAL should be adjusted. For patients discontinuing valproate, the dose of LAMICTAL should be doubled over a 2-week period in equal weekly increments (see Table 14). For patients discontinuing carbamazepine, phenytoin, phenobarbital, primidone, or rifampin, the dose of LAMICTAL should remain constant for the first week and then should be decreased by half over a 2-week period in equal weekly decrements (see Table 14). The dose of LAMICTAL may then be further adjusted to the target dose (200 mg) as clinically indicated.

Dosage adjustments will be necessary in most patients who start or stop estrogen-containing oral contraceptives while taking LAMICTAL (see DOSAGE AND ADMINISTRATION: Special Populations: Women and Oral Contraceptives: Adjustments to the Maintenance Dose of LAMICTAL).

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

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

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

*See CLINICAL PHARMACOLOGY: Drug Interactions and PRECAUTIONS: Drug Interactions for a description of known drug interactions.

†**Carbamazepine, phenytoin, phenobarbital, primidone**, rifampin, have been shown to increase the apparent clearance of lamotrigine.

‡**Valproate has been shown to decrease** the apparent clearance of lamotrigine.

Table 14. Adjustments to LAMICTAL Dosing for Patients With Bipolar Disorder 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

*See CLINICAL PHARMACOLOGY: Drug Interactions and PRECAUTIONS: Drug Interactions for a description of known drug interactions.

†**Carbamazepine, phenytoin, phenobarbital, primidone**, rifampin, have been shown to increase the apparent clearance of lamotrigine.

‡**Valproate has been shown to decrease** the apparent clearance of lamotrigine.

There is no body of evidence available to answer the question of how long the patient should remain on LAMICTAL therapy. Systematic evaluation of the efficacy of LAMICTAL in patients with either depression or mania who responded to standard therapy during an acute 8 to 16 week treatment phase and were then randomized to LAMICTAL or placebo for up to 76 weeks of observation for affective relapse demonstrated a benefit of such maintenance treatment (see

CLINICAL STUDIES: Bipolar Disorder). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

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

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

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

HOW SUPPLIED

LAMICTAL Tablets, 25-mg

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

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

LAMICTAL Tablets, 100-mg

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

LAMICTAL Tablets, 150-mg

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

LAMICTAL Tablets, 200-mg

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

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

LAMICTAL Chewable Dispersible Tablets, 2-mg

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

LAMICTAL Chewable Dispersible Tablets, 5-mg

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

LAMICTAL Chewable Dispersible Tablets, 25-mg

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

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

LAMICTAL Starter Kit for Patients Taking Valproate

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

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

LAMICTAL Starter Kit for Patients Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Rifampin and Not Taking Valproate

25-mg, white, scored, shield-shaped tablets debossed with "LAMICTAL" and "25" and **100-mg**, peach, scored, shield-shaped tablets **debossed with "LAMICTAL" and "100"**, blisterpack of 84, 25-mg tablets and 14, 100-mg tablets (NDC 0173-0594-01)

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

LAMICTAL Starter Kit for Patients Not Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone, Rifampin, or Valproate

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

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

PATIENT INFORMATION

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

Information for the Patient

LAMICTAL® (lamotrigine) Tablets

LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

ALWAYS CHECK THAT YOU RECEIVE LAMICTAL

Patients prescribed LAMICTAL (lah-**MICK**-tall) have sometimes been given the wrong medicine in error because many medicines have names similar to LAMICTAL. Taking the wrong medication can cause serious health problems. When your healthcare provider gives you a prescription for LAMICTAL

- make sure you can read it clearly.
- talk to your pharmacist to check that you are given the correct medicine.
- check the tablets you receive against the pictures of the tablets below. The pictures show actual tablet shape and size and the wording describes the color and printing that is on each strength of LAMICTAL Tablets and Chewable Dispersible Tablets.

LAMICTAL (lamotrigine) Tablets

 **25 mg, white Imprinted with LAMICTAL 25**	 **100 mg, peach Imprinted with LAMICTAL 100**	 **150 mg, cream Imprinted with LAMICTAL 150**	 **200 mg, blue Imprinted with LAMICTAL 200**

LAMICTAL (lamotrigine) Chewable Dispersible Tablets

 **2 mg, white Imprinted with LTG 2**	 **5 mg, white Imprinted with GX CL2**	 **25 mg, white Imprinted with GX CL5**

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

Information About Your Medicine:

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

1. The Purpose of Your Medicine:

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

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

If you are taking LAMICTAL to help prevent extreme mood swings, you may not experience the full effect for several weeks. Occasionally, the symptoms of depression or bipolar disorder may include thoughts of harming yourself or committing suicide. Tell your doctor immediately or go to the nearest hospital if you have any distressing thoughts or experiences during this initial period or at any other time. Also contact your doctor if you experience any worsening of your condition or develop other new symptoms at any time during your treatment.

Some medicines used to treat depression have been associated with suicidal thoughts and suicidal behavior in children or teenagers. LAMICTAL is not approved for treating children or teenagers with mood disorders such as bipolar disorder or depression.

2. Who Should Not Take LAMICTAL:

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

3. Side Effects to Watch for:

- Most people who take LAMICTAL tolerate it well. Common side effects with LAMICTAL include dizziness, headache, blurred or double vision, lack of coordination, sleepiness, nausea, vomiting, insomnia, and rash. LAMICTAL may cause other side effects not listed in this leaflet. If you develop any side effects or symptoms you are concerned about or need more information, call your doctor.
- Although most patients who develop rash while receiving LAMICTAL have mild to moderate symptoms, some individuals may develop a serious skin reaction that requires hospitalization. Rarely, deaths have been reported. These serious skin reactions are most likely to happen within the first 8 weeks of treatment with LAMICTAL. Serious skin reactions occur more often in children than in adults.
- Rashes may be more likely to occur if you: (1) take LAMICTAL in combination with valproate [DEPAKENE® (valproic acid) or DEPAKOTE® (divalproex sodium)], (2) take a higher starting dose of LAMICTAL than your doctor prescribed, or (3) increase your dose of LAMICTAL faster than prescribed.
- It is not possible to predict whether a mild rash will develop into a more serious reaction. **Therefore, if you experience a skin rash, hives, fever, swollen lymph glands, painful sores in the mouth or around the eyes, or swelling of lips or tongue, tell a doctor**

immediately, since these symptoms may be the first signs of a serious reaction. A doctor should evaluate your condition and decide if you should continue taking LAMICTAL.

4. The Use of LAMICTAL During Pregnancy and Breastfeeding:

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

5. Use of Birth Control Pills or Other Female Hormonal Products:

- Do not start or stop using birth control pills or other female hormonal products until you have consulted your doctor. Stopping or starting these products may-cause side effects (such as dizziness, lack of coordination, or double vision) or decrease the effectiveness of LAMICTAL.
- Tell your doctor as soon as possible if you experience side effects or changes in your menstrual pattern (e.g., break-through bleeding) while taking LAMICTAL and birth control pills or other female hormonal products.

6. How to Use LAMICTAL:

- It is important to take LAMICTAL exactly as instructed by your doctor. The dose of LAMICTAL must be increased slowly. It may take several weeks or months before your final dosage can be determined by your doctor, based on your response.
- Do not increase your dose of LAMICTAL or take more frequent doses than those indicated by your doctor. Contact your doctor, if you stop taking LAMICTAL for any reason. Do not restart without consulting your doctor.
- If you miss a dose of LAMICTAL, do not double your next dose.
- Always tell your doctor and pharmacist if you are taking any other prescription or over-the-counter medicines. Tell your doctor before you start any other medicines.
- Do NOT stop taking LAMICTAL or any of your other medicines unless instructed by your doctor.
- Use caution before driving a car or operating complex, hazardous machinery until you know if LAMICTAL affects your ability to perform these tasks.
- If you have epilepsy, tell your doctor if your seizures get worse or if you have any new types of seizures.

7. How to Take LAMICTAL:

LAMICTAL Tablets should be swallowed whole. Chewing the tablets may leave a bitter taste.

LAMICTAL Chewable Dispersible Tablets may be swallowed whole, chewed, or mixed in water or diluted fruit juice. If the tablets are chewed, consume a small amount of water or diluted fruit juice to aid in swallowing.

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

8. Storing Your Medicine:

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

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

If your doctor decides to stop your treatment, do not keep any leftover medicine unless your doctor tells you to. Throw away your medicine as instructed.

Manufactured for
GlaxoSmithKline
Research Triangle Park, NC 27709
by DSM Pharmaceuticals, Inc.
Greenville, NC 27834 or
GlaxoSmithKline
Research Triangle Park, NC 27709

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(Date of Issue) RL-

PHARMACIST--DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

Information for the Patient

LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

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- talk to your pharmacist to check that you are given the correct medicine.

- check the tablets you receive against the pictures of the tablets below. The pictures show actual tablet shape and size and the wording describes the color and printing that is on each strength of LAMICTAL Tablets and Chewable Dispersible Tablets.

LAMICTAL (lamotrigine) Tablets

 **25 mg, white Imprinted with LAMICTAL 25**	 **100 mg, peach Imprinted with LAMICTAL 100**	 **150 mg, cream Imprinted with LAMICTAL 150**	 **200 mg, blue Imprinted with LAMICTAL 200**

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- Rashes may be more likely to occur if you: (1) take LAMICTAL in combination with valproate [DEPAKENE® (valproic acid) or DEPAKOTE® (divalproex sodium)], (2) take a higher starting dose of LAMICTAL than your doctor prescribed, or (3) increase your dose of LAMICTAL faster than prescribed.
- It is not possible to predict whether a mild rash will develop into a more serious reaction. **Therefore, if you experience a skin rash, hives, fever, swollen lymph glands, painful sores in the mouth or around the eyes, or swelling of lips or tongue, tell a doctor immediately, since these symptoms may be the first signs of a serious reaction. A doctor should evaluate your condition and decide if you should continue taking LAMICTAL.**

4. The Use of LAMICTAL During Pregnancy and Breastfeeding:

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

5. Use of Birth Control Pills or Other Female Hormonal Products:

- Do not start or stop using birth control pills or other female hormonal products until you have consulted your doctor. Stopping or starting these products may cause side effects

(such as dizziness, lack of coordination, or double vision) or to decrease the effectiveness of LAMICTAL.

- Tell your doctor as soon as possible if you experience side effects changes in your menstrual pattern (e.g., break-through bleeding) while taking LAMICTAL and birth control pills or other female hormonal products.

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- Do not increase your dose of LAMICTAL or take more frequent doses than those indicated by your doctor. Contact your doctor, if you stop taking LAMICTAL for any reason. Do not restart without consulting your doctor.
- If you miss a dose of LAMICTAL, do not double your next dose.
- Always tell your doctor and pharmacist if you are taking any other prescription or over-the-counter medicines. Tell your doctor before you start any other medicines.
- Do NOT stop taking LAMICTAL or any of your other medicines unless instructed by your doctor.
- Use caution before driving a car or operating complex, hazardous machinery until you know if LAMICTAL affects your ability to perform these tasks.
- If you have epilepsy, tell your doctor if your seizures get worse or if you have any new types of seizures.

7. How to Take LAMICTAL:

LAMICTAL Tablets should be swallowed whole. Chewing the tablets may leave a bitter taste.

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

8. Storing Your Medicine:

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

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

If your doctor decides to stop your treatment, do not keep any leftover medicine unless your doctor tells you to. Throw away your medicine as instructed.

Manufactured for
GlaxoSmithKline
Research Triangle Park, NC 27709
by DSM Pharmaceuticals, Inc.
Greenville, NC 27834 or
GlaxoSmithKline
Research Triangle Park, NC 27709

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-241/S-027 and 20-764/S-020

MEDICAL REVIEW(S)

14 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

_____ Law Enforcement Action (b7)

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/s/

Philip Sheridan
9/27/2006 02:46:24 PM
MEDICAL OFFICER

John Feeney
9/29/2006 11:15:40 AM
MEDICAL OFFICER
Concur

Clinical Review of Partial Response to Approvable Letter

NDA (Serial Number)	**20-241/SEI-027 BZ**
Also referenced to:	**20-764/S-020**
	20-241/ (b) (4)
	20-764/ (b) (4)
	20-241/S-021
	20-764/S-014
	20-241/S-025
	20-764/S-018
	20-241/S-026
	20-764/S-019
Sponsor:	**Glaxo Smith Kline**
Drug:	**Lamictal (lamotrigine)**
Proposed Indication:	**Epilepsy**
Material Submitted:	**Partial response to approvable letter:**
	BA/BE, Clinical, Labeling
NDA Correspondence Date:	**March 22, 2006**
Date Received / Agency:	**March 23, 2006**
Date Review Completed	**September 15, 2006**
Reviewer:	**Philip H. Sheridan, M.D.**

1. Introduction

This submission is a partial response to the Agency's December 7, 2005 approvable letter for the applications referenced in the table below. These applications include both prior approval supplements and "Changes Being Effected" (CBE) supplements and are summarized in the table below.

Supplement Number	Submission Date	Provisions of Supplement
NDA 20-241/S-027 NDA 20-764/S-020	Feb 4, 2005	Prior approval supplement: adjunctive treatment of primary generalized tonic-clonic (PGTC) seizures
[redacted]		(b) (4)
NDA 20-241/S-021 NDA 20-764/S-014	May 29, 2003	CBE: Revised wording under PRECAUTIONS; Dermatologic Effects, DOSAGE AND ADMINISTRATION, Patient Information, and CLINCAL PHARMACOLOGY: Mechanism of Action
NDA 20-241/S-025 NDA 20-764/S-018	June 29, 2004	CBE: Revised wording under CLINICAL PHARMACOLOGY; Drug Interactions, and DOSAGE AND ADMINISTRATION
NDA 20-241/S-026 NDA 20-764/S-019	Aug 20, 2004	CBE: Revised Patient Information Leaflet

The current response is a partial one because the Sponsor has decided to postpone its response to two issues until a future submission. (b) (4) [redacted].

The Agency approvable letter's attached labeling contained a number of important labeling changes that are not at issue now. **These important changes are not highlighted in the revision-marked labeling now submitted by the Sponsor** since the Sponsor is using the Agency's proposed language from the approvable letter as the base document rather than the currently approved labeling. All the cumulative changes will appear if and when an approval letter is issued by the Agency because the base document then used will be the currently approved labeling. The important changes not high-lighted include the new indication (adjunctive therapy in pediatric and adult patients with primary generalized tonic-clonic seizures) and a description of the study supporting this indication, a section on possible restarting of Lamictal after discontinuation due to rash, and editorial changes to the black box warning, to the mechanism of action section, to the drug interactions section, to the dosage and administration section, and to tables 1, 2, 3, 4, 9, 10, 11, and 12. **Section 8 of my review addresses a change to a column heading in Tables 9 and 11 that the Sponsor did not make in response to the approvable letter but should have.**

In the topical sections 2 through 7 of this review, Agency comments from the approvable letter are provided first, followed by GSK's response in this

submission, and then followed by my bolded-and-italicized ***Reviewer's Comment*** on the GSK response.

(b) (4)

3. Oral Contraceptives

Agency Comment 2:

The Agency commented that the recommendation that maintenance doses of LAMICTAL may need to be twice the recommended doses in women receiving oral contraceptives may give rise to clinical scenarios for which tolerability data are not available. Specifically, making the dose for these women twice as high as the recommended dose could result in an adjunctive Lamictal dosage as high as 750 mg/day for patients receiving non-inducing/noninhibiting AEDs and as high as 1000 mg/day for patients on Lamictal monotherapy.)

In addition, for the conversion to monotherapy setting, the Agency requested that GSK provide guidance in decreasing LAMICTAL to a dose of 500 mg daily for patients on oral contraceptives who may be receiving higher doses.

Finally, because of the possibility of increases in lamotrigine levels and adverse events during the “pill-free” week, the Agency requested that this phenomenon be more prominently described in labeling.

GSK Response: A summary of the available data on the tolerability of LAMICTAL at doses or dose equivalents greater than 500 mg/day and on the tolerability of LAMICTAL in women who are also taking oral contraceptives is provided in **Module 5.3.5.3.** . The following data sources are summarized:

Tolerability of doses >500mg/day

- Data from clinical trials US17 and US26, sponsored by GlaxoSmithKline

- Data from a database of epilepsy patients, maintained by the Comprehensive Epilepsy Center at Columbia University, New York, New York

Tolerability of LAMICTAL in women who are also taking an oral contraceptive

- Data evaluated from the Comprehensive Epilepsy Center at Columbia University

- Data collected from patients in the clinical development program for bipolar disorder

Collectively these sources document an increasing incidence of nonserious CNS adverse events (primarily dizziness and ataxia) with increasing exposure to LAMICTAL. These events have previously been identified as dose-related adverse events associated with the use of LAMICTAL and are nonserious, predictable and easily managed clinically.

These data provide the rationale to support the currently refined dosing recommendations contained within this response for increasing and decreasing the dose of LAMICTAL in situations where the maintenance dose exceeds the current recommended maximum of 500 mg/day and for the use of LAMICTAL in women who are also taking oral contraceptives.

(b) (4)

These recommendations are similar to what is being proposed for the US label.

Reviewer's Comment:

Tolerability of doses >500mg/day

- **Data from clinical trials US17 and US26, sponsored by GlaxoSmithKline**

The lamotrigine serum levels from these two studies represent the highest exposures to Lamictal for any GSK-sponsored study.

US 17 was an open-label continuation study providing up to 288 additional weeks of treatment in adults who had been in one of five controlled trials or four open-label continuation trials of adjunctive Lamictal for partial seizures. The maximum dose was 750 mg/day. Patients were assessed every 6 months. 527 subjects participated of whom only 197 had a serum level and demographic data. These 197 were used for this safety analysis.

US 26 was an open-label study to provide Lamictal to patients age 1 year and older with serious or life-threatening epilepsy. Dosage was tailored to the patient at the discretion of the investigator.

1066 patients participated of whom only 427 had a serum level and demographic data. These 427 were used for this safety analysis

Therefore, the Sponsor has used 624 patients (197 from #17 and 427 from #26, assuming that serum levels are a better indication than dosage of Lamictal exposure given the variety of adjunctive medications in the study populations.

Two further assumptions were made: (1) that comparison of the adverse effects should be made between lamotrigine concentrations above and below 10 ug/ml since this concentration corresponds to a Lamictal dose of about 600 mg/day, and (2) the linear relationship observed between Lamictal dose and steady-state serum concentrations at doses up to 700 mg/day will continue to be linear at doses above 700 mg/day [as evidenced by data published in Hirsch LJ, 2004 discussed below]; specifically, this would mean steady-state concentrations greater than 16 ug/ml would approximate a Lamictal Monotherapy dose of at least 1000 mg/day.

Considering the 624 patients, looking at Table 4 (page 20 of Module 5.3.3.3)

Of 197 patients in Study 17,
142 (71%) had conc <10 mcg/ml (approximating <600 mg/day)
35 (17%) had conc 10-<15 mcg/ml (approx 600-1000 mg/day)
20(10%) had conc 15->20 mcg/ml (approx 1000 plus mg/day

Of the 427 in Study 26
350 (82%) had conc <10 mcg/ml (approximating <600 mg/day)
53 (12%) had conc 10-<15 mcg/ml (approx 600-1000 mg/day)
24 (6%) had conc 15->20 mcg/ml (approx 1000 plus mg/day

Of the total 624 patients
492 (79 %) had conc <10 mcg/ml (approximating <600 mg/day)
88 (14 %) had conc 10-<15 mcg/ml (approx 600-1000 mg/day)
44 (7 %) had conc 15->20 mcg/ml (approx 1000 plus mg/day

Thus, between studies 17 and 26, 132 patients had serum levels corresponding to a dose of 600-1000 plus mg/day and 44 of these 132 had levels corresponding to a dose of >1000 mg/day.

Table 6 similarly divides these patients into <10 mcg/ml [n=492] or ≥ 10 mcg/ml [N=132 as above] for all adverse events and Table 7 does the same for all serious adverse events. The incidence of adverse effects is higher in the higher serum level group (34% compared to 26%) but similar in nature. Table 7 indicates the serious adverse events were about the same in both groups (3% for the ≥ 10 mcg/ml group and 4% for the <10 mcg/ml). Some were probably not drug related. There were no serious rashes or fatalities.

• Data from a database of epilepsy patients, maintained by the Comprehensive Epilepsy Center at Columbia University, New York, New York

This data is taken from an article published by Dr. Lawrence J. Hirsch and colleagues at Columbia University (Neurology 2004;63:1022-1026) entitled "Correlating lamotrigine serum concentrations with tolerability in patients with epilepsy".

The abstract is as follows:

OBJECTIVE: To correlate lamotrigine (LTG) serum concentrations (levels) with tolerability in patients with epilepsy. METHODS: The charts of 811 outpatients with epilepsy who had received LTG and were seen at the Columbia Comprehensive Epilepsy Center after January 1, 2000, were reviewed. Data gathered included levels, dosage, duration of use, concomitant antiepileptic drugs (AEDs), clinical toxicity, specific side effects, and efficacy. Rates of toxicity, specific side effects, and efficacy were calculated and correlated with serum levels. RESULTS: In total, 3,731 LTG levels were recorded. A regimen was categorized as toxic if the patient experienced side effects that led to a dosage change or discontinuation of LTG. Of 3,919 AED regimens, 9.4% were toxic and 30.7% of patients had at least one toxic regimen. Toxicity increased with increasing LTG levels ($p < 0.0001$): With levels <5.0 microg/mL, 7% of patients were toxic; with levels of 5 to 10 microg/mL, 14%; with 10 to 15 microg/mL, 24%; with 15 to 20 microg/mL, 34%; and with >20 microg/mL, 59%. The correlation between levels and tolerability was independent of concurrent medication. Increasing efficacy, as measured by seizure freedom for a 6-month period, occurred

up to levels of >20 microg/mL. CONCLUSIONS: There is a correlation between LTG serum level and tolerability, independent of the use of other AEDs. Adverse effects requiring a dose change are uncommon with the most frequently encountered LTG concentrations (<10 microg/mL) and occur in only 7.4% of patients at levels obtained during the majority of clinical trials (<5 microg/mL). An initial target range of 1.5 to 10 microg/mL is suggested, though higher levels, up to >20 microg/mL, are often tolerated and can lead to additional efficacy in refractory patients.

Although the abstract refers to 811 patients, the analysis in the article was on the 714 patients (88% of all patients in the Columbia database) and their 2,654 regimens for which both toxicity status and blood levels (a total of 3,731 levels) were available.

The clinical pharmacology review summarized the correlation of serum levels and toxicities in this article in the following table.

Lamotrigine Serum Concentrations	Corresponding Doses (mg/day)	% of Regimens Toxic	% of Patients Toxic	Seizure-free for ≥6 months
<5 µg/mL	<300	4.3% (n = 975)	7.1% (n = 462)	42.9% (n = 112/261)
5 ~ 9.9 µg/mL	300 ~ 600	7.7% (n =1024)	14.3% (n = 460)	41.2% (n = 121/294)
10 ~ 14.9 µg/mL	600 ~ 900	15.9% (n = 421)	24.2% (n = 231)	40.1% (n = 65/162)
15 ~ 19.9 µg/mL	900 ~ 1200	26.7% (n = 105)	33.8% (n = 71)	29.1% (n = 16/55)
>20 µg/mL	>1200	52.4% (n = 21)	59% (n = 17)	14.3% (n = 2/14)

A toxic regimen was defined as one requiring a dose change or change to another antiepileptic drug. As with the Sponsor's experience in studies 17 and 26, the patients in the Columbia database have more toxic side effects at the higher serum levels but the adverse effect were similar (mostly the CNS-related effects of imbalance, dizziness, and drowsiness) and reversible There were no serious rashes and no deaths.

At the request of the Sponsor, Dr. Hirsch has updated the data in a report dated February 10, 2006. The results are very similar to those he had previously published. A total of 267 patients are now reported to have had lamotrigine concentrations in the range of 10-14.9 ug/ml (corresponding to estimated doses of 600 to 900 mg/day. 26.5% of patients had adverse effects attributable to Lamictal and 18.7% had adverse effects significant enough to require dose adjustment or discontinuation. The most common adverse effects again were imbalance (7.8%), dizziness (4.1%), and drowsiness (3.7%).

Tolerability of LAMICTAL in women who are also taking an oral contraceptive

• Data evaluated from the Comprehensive Epilepsy Center at Columbia University

There were 288 women between the age of 16 and 56 years in the database. Of these, 24 were on oral contraceptives at some time during data collection, 4 of them being on the OCs continuously. There were 31 different observations of level-toxicity (refereed to as patient-level observations by the Sponsor) for the 24 women of OCs and 443 patient-level observations among the 264 women not on OCs. The frequency of toxicity was higher among women not on the OCs (18.1% overall, 38.5 monotherapy) compared to the women on OCs (6.3% overall, 12.5% monotherapy). Since the women on oral contraceptives did not have their doses doubled, they probably had lower Lamictal serum levels due to the interaction with the contraceptives and this may explain why their toxicity was lower than that of women not on oral contraceptives. The data does not address the pill-free week.

• Data collected from patients in the clinical development program for bipolar disorder

The sponsor conducted a retrospective analysis of safety data from long-term controlled studies, acute controlled studies, and uncontrolled adjunctive therapy studies in women with bipolar disorder. The only adverse effect occurring with higher incidence in women on OCs was diarrhea. This data is of less usefulness because (1) the dosage for bipolar disorder

is usually less than for epilepsy, (2) the women on oral contraceptives did not have their Lamictal doses increased in these studies as ins now proposed, (3) the "pill-free" week was not noted in data collection.

In summary, the combined data sources indicate that, although the dose-related adverse effects increase at doses greater that 500-600 mg/day, these effects do not occur in most patients, are typical side effects for Lamictal, and are reversible.

(b) (4)

The Sponsor has provided proposed revised labeling regarding oral contraceptives for the drug interactions section (p. 20 of the Sponsor's annotated revision-marked proposed labeling) and for the DOSAGE AND ADMINISTRATION section (p. 40 of the Sponsor's annotated revision-marked proposed labeling). These are prominent and clearly written. They appropriately address the clinical scenarios raised in the Agency's approvable letter.

The clinical pharmacology reviewer agrees with these conclusions but makes the additional point that non-ethinylestradiol containing oral contraceptives [the Progestin Only Pills or POPs] are reported not to affect the clearance of lamotrigine. Therefore OCP suggests amended language to the labeling proposed by the Sponsor to address this difference in oral contraceptives.

4. Replacement of "Enzyme-Inducing AEDs" with Specific Drug Names

Agency Comment 3:

We do not believe that this substitution is appropriate in those sections pertaining to dosing in patients with bipolar disorder. In these patients, we would not expect that most of the specific AEDs named are relevant. Further, (b) (4)

(b) (4)

Removing the “enzyme-inducing” drugs language may be problematic in this regard.

Finally, the Agency requested that GSK consider explicitly referring to the enzyme system (UDP-glucuronyl-transferase) involved with metabolism of lamotrigine, as clinicians may interpret the phrase “enzyme-inducing drug as pertaining to the CYP450 enzyme system.

GSK Response:

GlaxoSmithKline recognizes that patients with epilepsy and bipolar disorder are often treated with medications including antiepileptic drugs (AEDs) that might induce or inhibit the metabolism of lamotrigine. Nevertheless, defining a compound as either an “enzyme inducer” or an “enzyme inhibitor” would not necessarily obviate the potential for confusion as it is possible that the drugs classified or assumed to be an inducer or inhibitor hepatic enzymes may not specifically interact with lamotrigine. For this reason, GSK believes that the most appropriate way of categorizing the dosing recommendations for both epilepsy and bipolar disorder is based on specific drugs where the interaction with lamotrigine has been established. Therefore, GSK proposes that the dosing categories based on specific drugs as presented in current in-use labeling be maintained.

The dosing recommendations for LAMICTAL for epilepsy were based on ***concomitant AED therapy*** rather than non-AED therapy, despite the fact that other non-AED therapy may induce or inhibit lamotrigine metabolism. However, it is not practical to evaluate every possible drug interaction with lamotrigine. Thus, prior to the submission of NDA 20-241/S-027 and NDA 20-764/S-020, labeling for LAMICTAL recommended use of the more conservative guidelines for adding LAMICTAL to valproate in instances where the interaction of LAMICTAL and other drugs is unknown. An intermediate dosing regimen for adding LAMICTAL to AEDs other than VPA or EIAEDs that was utilized in LAM40097 is provided in proposed labeling. As noted in section 4.2.2 of the Clinical Overview for NDA 20-241/S-027 and NDA 20-764/S-020, the rationale for this regimen (which is also recommended for initial monotherapy with LAMICTAL in countries where this indication is approved) was based on published and unpublished data demonstrating either a lack of interaction with lamotrigine or evidence that such an interaction either does not occur or its occurrence is very unlikely. Thus it would be expected that these drugs given with LAMICTAL would have similar plasma concentrations to those seen when LAMICTAL is administered alone. These same recommendations and drug categories were utilized previously in the clinical program for evaluating LAMICTAL in bipolar disorder and were subsequently approved in April 2003.

With the submission of NDA 20-241/S-025 and NDA 20-764/S-018 on June 29, 2004, GSK implemented the use of specific AED names rather than general categories based on the results of a study evaluating the interaction of lamotrigine and oxcarbazepine (SCA10910). Because oxcarbazepine is chemically related to carbamazepine, clinicians assumed this drug was also an inducer of lamotrigine metabolism and utilized the dosing recommendations for adding LAMICTAL to EIAEDs. However, the results of this study demonstrated a lack of effect of oxcarbazepine and GSK was concerned that utilization of these guidelines rather than the more conservative intermediate regimen would increase the risk of serious rash in patients receiving concomitant LAMICTAL and oxcarbazepine. Based on this experience, GSK believed that the best way to present the dosing recommendations for LAMICTAL was to categorize dosing recommendations based on drugs where the interaction was known and utilizing the intermediate regimen for addition of LAMICTAL for drugs where the interaction was unknown. While there may be some instances where LAMICTAL is added to a possible inducer of lamotrigine metabolism, GSK believes that use of more conservative guidelines may reduce the risk for serious rash, although it may require a longer period to achieve a therapeutic dose.

With regard to the use of the same drug categories for both epilepsy and bipolar disorder, we are not aware of any confusion among psychiatrists with the use of specific drug names rather than general categories of enzyme-inducing and inhibiting drugs. Furthermore, consideration must be give to the sample titration kits and prescription starter kits that have been developed by GSK as a means of reducing the risk for serious rash as well as medication errors. These kits correspond to the dosing categories presented in current in-use labeling and are used by both psychiatrists and neurologists to initiate therapy with LAMICTAL. Changes to the dosing categories for bipolar disorder could result in confusion among psychiatrists as to the proper kit to utilize. Furthermore, development of kits with different dosing categories for epilepsy and bipolar disorder would result in even more confusion.

Finally, GSK agrees that the average prescriber may interpret the descriptor, “enzyme- inducing drug,” as being reflective of the CYP450 enzyme system and not the UDP- glucuronyl-transferase system, the system which is responsible for the metabolism of lamotrigine. However, drugs known to affect UDP-glucuronyl-transferase, including rifampin and carbamazepine, can also affect CYP450. Thus, it may not be helpful to include this specific statement in labeling, as enzyme-inducing and inhibiting drugs may have effects on multiple enzyme systems.

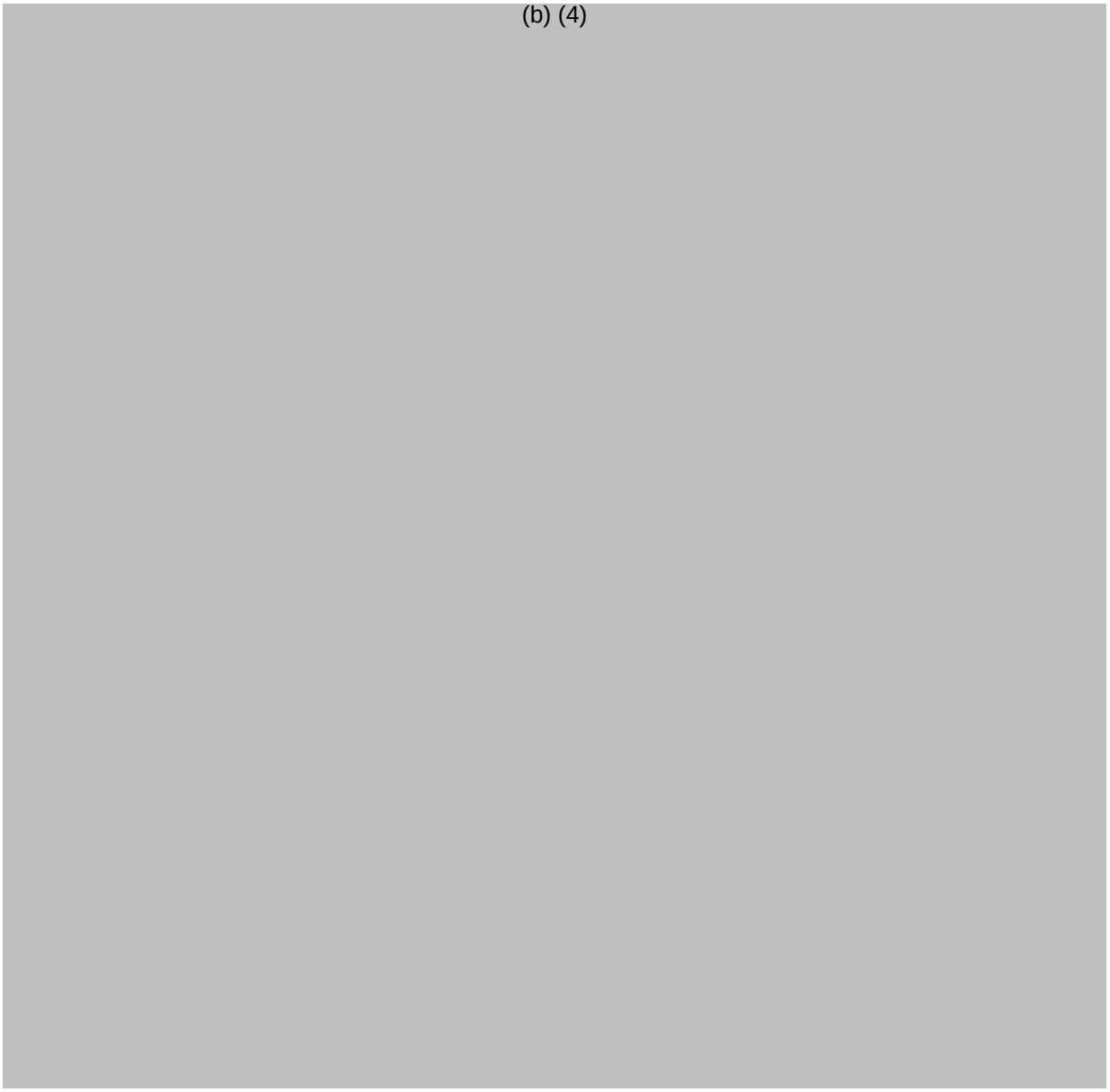
Reviewer Note:

GSK again proposes to replace the phrase “enzyme-inducing drugs” with specific lists of such AEDs (as well as rifampin). GSK argues that even neurologists may not know which antiepileptic drug is an inducer and

which is not (e.g. carbamazepine is but oxcarbazepine is not). The Agency remains concerned that there are other (non-AED) enzyme-inducing drugs especially in the nonepileptic population (e.g. bipolar patients). Both GSK and the Agency are concerned that the phrase "enzyme-inducing drug" would imply a drug inducing the CYP450 system to most prescribers even though it is induction of the UDP-glucuronyl-transferase system that increases Lamictal's clearance.

Perhaps the best solution is the middle ground. Listing specific AEDs is reasonable. Other commonly used non-AED drugs like rifampin known to have a similar effect could also be listed along with a sentence indicating that other non-AEDs might have a similar effect if they induce the UDP-glucuronyl-transferase system.

(b) (4)



6. Drug-Drug Interactions

Agency Comment 5:

We ask that you formally study the interaction of lamotrigine with tiagabine. You should also further address the potential for interaction between lamotrigine and gabapentin and between lamotrigine and pregabalin.

GSK Response:

Tiagabine

Based on the following information, GSK believe that the rationale for performing a formal drug-drug interaction study based on pharmacokinetic grounds alone is limited, as a clinically significant pharmacokinetic interaction between lamotrigine and tiagabine is unlikely.

Lamotrigine is hepatically metabolized primarily by glucuronic acid conjugation (UGT1A4). The major metabolite is an inactive 2-N-glucuronide conjugate. Following oral administration of 240 mg of 14C-lamotrigine to healthy volunteers (N=6), 94% of drug related material was recovered in urine and 2% was recovered in feces. The urinary contents consisted of unchanged lamotrigine (10%), the 2-N-glucuronide (76%), a 5-N- glucuronide (10/o), a 2-N-methyl metabolite (0.14%) and another unidentified minor metabolite (4%). Consistent with this, lamotrigine clearance is decreased when it is co- administered with the glucuronidation inhibitor, valproate. Hepatic enzyme-inducing agents increase the clearance of lamotrigine. Drugs such as carbamazepine, phenytoin, phenobarbital or primidone, rifampin, and oral contraceptives are believed to achieve this by induction of glucuronidation capacity.

Lamotrigine has been shown to have no appreciable effect on the clearance of phenytoin (primarily metabolized by oxidation, CYP2C, some glucuronidation), nor on carbamazepine (oxidation, CYP3A & CYP2C and glucuronidation), oxcarbazepine or levetiracetam. A small, but clinically insignificant decrease in valproate exposure was observed (-25%) in healthy volunteers. In patients, no change in valproate plasma concentrations in either adults or pediatric patients was observed in controlled clinical trials when coadministered with LAMICTAL.

Tiagabine is primarily cleared by hepatic metabolism via oxidation of the thiophene rings and to a small extent glucuronidation. In contrast to lamotrigine the clearance of tiagabine was unaffected when coadministered with valproate supporting evidence that glucuronidation is a minor route in the clearance of

tiagabine. In-vivo, the clearance of tiagabine has been shown to be significantly increased when coadministered with hepatic enzyme-inducing drugs such as carbamazepine, phenytoin, phenobarbital or primidone which is believed to be achieved by the induction of CYP3A capacity [Brodie et al, 1995; Samara et al, 1998]. Similar to lamotrigine, little or no effect of tiagabine has been observed on the clinical pharmacokinetics of enzyme-inducing AEDs (phenytoin, carbamazepine, phenobarbital or primidone) or valproate (about 10% decrease in steady-state valproate concentrations was observed).

In terms of safety and tolerability with coadministration of tiagabine and LAMICTAL, we believe it is unlikely that the safety/tolerability profile is altered during coadministration in comparison to the profile associated with each drug respectively.

In conclusion, given the apparent minor role of glucuronidation in the clearance of tiagabine as indicated by the lack of pharmacokinetic interaction with valproate and the lack of effect of enzyme inhibition/induction potential of lamotrigine, there is a low likelihood of tiagabine inducing or inhibiting the metabolism of lamotrigine under steady- state lamotrigine conditions or of lamotrigine inhibiting or inducing the metabolism of tiagabine, leading to a clinically significant change in clearance. For this reason, a specific drug-drug interaction study is not planned.

Reviewer Comment:

The clinical pharmacology reviewer accepts GSK's argument.

Gabapentin

Gabapentin has a similar disposition to pregabalin in terms of low protein binding (<3%) and high renal clearance. Healthy volunteer studies with common AEDs which are known to induce or inhibit 3A and UGT metabolism had no effect on the clearance of gabapentin. Furthermore, pharmacokinetic analysis of gabapentin in patients receiving gabapentin for at least 3 months, on a range of doses of 400-4000 mg/day, revealed that coadministration with lamotrigine had little or no effect on gabapentin concentrations and these were higher than the gabapentin concentration ran e observed when coadministered with phenytoin, carbamazepine and valproate [May et al, 1997]. In terms of the effects of gabapentin on the clearance of lamotrigine, a recent retrospective review article of the effect of antiepileptic drugs on the clearance of lamotrigine was investigated in a retrospective anal sis, using the data from 570 medical charts of outpatients with epilepsy ($\geq$ 12 years) [Weintraub et al, 2005]. They reported the mean clearance to be between 93 and 97% of the monotherapy value when coadministered with gabapentin, with the ratios being based on both within and between patient comparisons. The mean clearance in patients (N=34) taking lamotrigine alone was reported to be 39.9 ml/h/Kg versus 38.9 ml/h/Kg when coadministered with gabapentin in the same patients. Between patient

comparisons were also made based on data from 97 patients. The mean clearance of lamotrigine monotherapy was 43.2 ml/h/kg (n=409), and in a separate group of patients taking lamotrigine in combination with gabapentin was 40 ml/min/kg (n=97). Therefore, the likelihood of either lamotrigine causing inhibition or induction of the clearance of gabapentin or gabapentin inducing or inhibiting the clearance of lamotrigine is minimal.

In conclusion, the probability of a drug interaction between LAMICTAL and gabapentin is considered minimal and would likely not be clinically significant. Proposed labeling for LAMICTAL includes a summary of the published information by Weintraub et al [Weintraub et al, 2005].

Reviewer Comment:

The clinical pharmacology reviewer accepts GSK's argument.
Pregabalin

The prescribing information for pregabalin states that "steady-state trough plasma concentrations of lamotrigine were not affected by concomitant pregabalin (200 mg three times a day) administration." It also reports that lamotrigine has no effect on the pharmacokinetics of pregabalin.

GSK will incorporate this information verbatim into proposed labeling for LAMICTAL.

Reviewer Note:

The Pregabalin approved labeling does have this language under CLINICAL PHARMACOLOGY. The Sponsor's proposal is acceptable to me and the clinical pharmacology reviewer agrees.

7. Labeling

GSK are providing revised proposed labeling using the base copy with all FDA requested changes that was provided with the December 7, 2005 approvable letter. The GSK-proposed labeling text shows revisions by underlines and deletions by strikethroughs and is annotated to accompanying supporting documentation.

GSK will provide labeling in SPL format at the time that labeling text has been finalized. The base copy for the SPL version will be the current in use base copy.

The following sections of proposed labeling have been revised. A number of these revisions are in response to comments received in the approvable letter and the NOTES TO SPONSOR imbedded within the draft labeling provided in the Agency's approvable letter.

CLINICAL PHARMACOLOGY

Drug Interactions: As requested by the Agency, information regarding felbamate, gabapentin, pregabalin, topiramate, and zonisamide has been added.

Reviewer Note:

These appear appropriate to me and to the clinical pharmacology reviewer.

Hepatic Disease: GSK has adopted wording for this section as provided in the Agency's December 3, 2002 approvable letter for NDA 20-241/S-010 and NDA 20-764/S-003.

Race: The Agency noted that in its analysis of LAM40097, Black patients had trough plasma concentrations at week 19 that were 79% higher than Hispanic patients and 41% higher than white patients. The agency asked that GSK address this finding in light of current labeling which states that the apparent clearance for lamotrigine was 25% lower in non-Caucasians than Caucasians.

While the observation that the mean lamotrigine trough concentrations at week 19 or 24 are 79% higher than Hispanic patients and 41% higher than White patients is correct, these concentration data must be considered in the light of concomitant medications as, for all groups, higher lamotrigine concentrations were observed with concomitant VPA than with either of the other dosing groups. Among Black patients 5/7 or 71% were taking concomitant VPA while only 36% and 46% of Hispanic and white patients respectively were taking concomitant VPA. The mean lamotrigine concentration for black patients taking concomitant VPA was 7.2 mcg/ml (n=5) compared with 6.8 mcg/ml for White patients (n=11) and 5.2 mcg/ml for Hispanic patients (n=5). The other two Black patients were both taking concomitant enzyme inducing AEDs and had a mean concentration of 4.9 mcg/ml which was higher than the Hispanic (n=8, 2.6 mcg/ml) or the White (n=10, 2.7 mcg/ml) patients. However one of the two Black patients had a concentration of 1.5 mcg/ml while the other had a concentration of 8.5 mcg/ml. GSK believes the differences in the number of patients using concomitant VPA across these racial groups accounts for most of the difference in lamotrigine serum concentrations observed in this study.

In contrast, the wording in current labeling in based on a population pharmacokinetic analysis of patients who participated in Phase 2 and Phase 3 clinical trials of LAMICTAL during the original clinical development program (report submitted to NDA 20-241 on May 25, 1993). Because this analysis included patients from multiple studies, GSK believes this is a more appropriate reflection of the effect of race on lamotrigine clearance. For this reason, we propose maintaining the current wording.

Reviewer Note:

This argument seems reasonable to me and is accepted by the clinical pharmacology reviewer.

(b) (4)

PRECAUTIONS
Concomitant Use with Oral Contraceptives: New subsection advising clinicians about the possible need for dosage adjustments and the possible occurrence of adverse events during the "pill-free" week adverse events has been added at the Agency's request.

Reviewer Note:

This language is clear and appropriate as proposed; it effectively addresses the scenarios of concern discussed in the approvable letter.

Drug Interactions: Information regarding the interaction of lamotrigine with felbamate, gabapentin, pregabalin, topiramate, and zonisamide has been added at the Agency's request. Table 3 of labeling has been revised to incorporate this additional information.

Reviewer Note:

These appear appropriate to me and are acceptable to the clinical pharmacology reviewer.

(b) (4)

Special Populations: Women and Oral Contraceptives: At the Agency's request, this subsection has been revised to provide more specific information on increasing the maintenance dose of LAMICTAL in women also receiving oral contraceptives, guidance on adjustments to the maintenance dose during the pill-free week in cases where adverse events occur consistently during this period, and guidance on decreasing the maintenance dose of LAMICTAL in women stopping oral contraceptives.

Reviewer Note:

The clinical pharmacology reviewer makes the point that non-ethinylestradiol containing oral contraceptives [the Progestin Only Pills or POPs] are reported not to affect the clearance of lamotrigine. Therefore OCP suggests amended language to the labeling proposed by the Sponsor to address this difference in oral contraceptives.

The prominence of the discussion of the interaction between Lamictal and oral contraceptives might need to be increased either by making it a warning or bolding the PRECAUTIONS and DOSAGE AND ADMINISTRATION sections. The wording for the recommended course of action (doubling the dose of Lamictal) may need to be strengthened from the current wording "maintenance dose may need to be increased by as much as 2-fold over the recommended target maintenance dose, based on clinical response" to more directive wording such as "should be doubled".

Special Populations: Patients with Hepatic Impairment: GSK has adopted the categories of impairment noted in the Agency's December 3, 2002 approvable letter. However, GSK believes that the (b) (4) in NDA 20-241/S-010 and NDA 20-764/S-003 is appropriate. A justification for maintaining these guidelines is provided in an attachment (attachment 2 of the cover letter).

Reviewer's Note:

In attachment 2 to the cover letter, the Sponsor accepts the Agency's original 2002 language for the following section

> ***CLINICAL PHARMACOLOGY-Hepatic Disease:***
> ***The pharmacokinetics of lamotrigine following a single 100-mg dose of LAMICTAL were evaluated in 24 subjects with mild, moderate, and severe hepatic dysfunction (Child-Pugh Classification system) and compared with 12 subjects without hepatic impairment. The patients with severe hepatic impairment were without ascites (n = 2) or with ascites (n = 5). The mean apparent clearance of lamotrigine in patients with mild (n = 12), moderate (n = 5), severe without ascites (n = 2), and severe with ascites (n = 5) liver impairment was 0.30 ± 0.09, 0.24 ± 0.1, 0.21 ± 0.04, and 0.15 ± 0.09 mL/min/kg, respectively, as compared to 0.37 ± 0.1 mL/min/kg in the healthy controls. Mean half-life of lamotrigine in patients with mild, moderate, severe without ascites, and severe with ascites liver impairment was 46 ± 20, 72 ± 44, 67 ± 11, and 100 ± 48 hours, respectively, as compared to 33 ± 7 hours in healthy controls (for dosing guidelines, see DOSAGE AND ADMINISTRATION: Patients With Hepatic Impairment).***

However, the Sponsor proposes to revise the guidelines in DOSAGE AND ADMINISTRATION: Patients with Hepatic Impairment as shown (with the base language being the Agency's December 3, 2002 wording).

(b) (4)

(b) (4)

(b) (4)

. This is a logical argument that is acceptable to me and to the clinical pharmacology reviewer.

PATIENT INFORMATION LEAFLET
Addition of possible side effects that could occur when oral contraceptives are started and stopped in patients receiving concomitant LAMICTAL and oral contraceptives.

Reviewer Note:

The Sponsor proposes to simplify the Agency's proposed language.

(b) (4)

This change is acceptable.

8. Tables 9 and 11 Escalation Regimens

In the approvable letter, the Agency asked the Sponsor to change the column positions in Table 9. The Agency also asked that the heading of one of the columns be reworded so that it would not be misinterpreted as referring to initial monotherapy with Lamictal since Lamictal does not have an initial monotherapy indication. A similar rewording was requested for a column heading in Table 11.

In the proposed labeling in the partial response, the Sponsor changed the column positioning Table 9 but retains the wording of column heading in Tables 9 and 11 as follows: (b) (4)

Again, in order to avoid confusion with initial monotherapy with Lamictal, the column heading should be changed to "For Patients Taking AEDs other than Carbamazepine, Phenytoin, Phenobarbital, Primidone* and Not taking Valproate".

9. Reviewer Conclusion and Recommendation

In general, this partial response to the approvable letter is responsive to the concerns of the Agency.

The clinical pharmacology reviewer makes the point that non-ethinylestradiol containing oral contraceptives [the Progestin Only Pills or POPs] are reported not to affect the clearance of lamotrigine. Therefore OCP suggests amended language to the labeling proposed by the Sponsor to address this difference in oral contraceptives.

The prominence of the discussion of the interaction between Lamictal and oral contraceptives might need to be increased either by making it a warning or bolding the PRECAUTIONS and DOSAGE AND ADMINISTRATION sections. The wording for the recommended course of action (doubling the dose of Lamictal) may need to be strengthened from the current wording “maintenance dose may need to be increased by as much as 2-fold over the recommended target maintenance dose, based on clinical response” to more directive wording such as “should be doubled”.

In Tables 9 and 11, in order to avoid confusion with initial monotherapy with Lamictal, the column heading should be changed to “For Patients Taking AEDs other than Carbamazepine, Phenytoin, Phenobarbital, Primidone* and Not Taking Valproate”.

(b) (4)

Philip Sheridan, M. D.
Medical Reviewer

cc: NDA 20-241
HFD 120 Division File
HFD 120/Calder /Feeney/Sheridan/Katz

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/s/

Philip Sheridan
9/27/2006 02:40:49 PM
MEDICAL OFFICER

John Feeney
9/29/2006 11:14:08 AM
MEDICAL OFFICER
I concur with Dr.Sheridan. See my cover memo dated December 5, 2005 for my prior discussion of these issues. Labeling was negotiated with the sponsor to reflect a prominent Precaution about the concomitant use with estrogen-containing oral contraceptives.

MEMORANDUM

DATE: December 8, 2005

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 20-241/S-027 & NDA 20-764/S-020

SUBJECT: Action Memo for NDA 20-241/S-027, Lamictal (lamotrigine) Tablets and NDA 20-764/S-020, Lamictal (lamotrigine) Chewable Dispersible Tablets, for the use of Lamictal as adjunctive treatment for Primary Generalized Tonic-Clonic Seizures and NDA 20-241/ (b) (4) Lamictal Tablets and NDA 20-764/ (b) (4) Lamictal Chewable Dispersible Tablets, (b) (4)

NDA 20-241/S-027, Lamictal (lamotrigine) Tablets and NDA 20-764/S-020, Lamictal (lamotrigine) Chewable Dispersible Tablets, for the use of Lamictal as adjunctive treatment for Primary Generalized Tonic-Clonic Seizures and NDA 20-241/ (b) (4) Lamictal Tablets and NDA 20-764/ (b) (4) Lamictal Chewable Dispersible Tablets, (b) (4) , were submitted by GlaxoSmithKline on (b) (4) . These supplements contain, respectively, the results of a single randomized controlled study (Study LAM 40097), and pharmacokinetic data (both from this study as well as from other sources). Currently, Lamictal is approved as adjunctive therapy for partial seizures in adults and pediatric patients, as well as for the generalized seizures of Lennox-Gastaut syndrome in adults and pediatric patients. It is also approved for conversion to monotherapy in adults already being treated with enzyme-inducing AEDs and in adults already being treated with valproate (with our without EIAEDs). It is not approved for use as initial monotherapy.

In addition to the supplements described, the sponsor has previously submitted numerous Changes Being Effected (CBE) supplements that have a bearing on the current supplements. Specifically, the following CBE supplements have relevance:

20-241/S-021 & 20-764/S-014; submitted 5/29/03-Proposes various labeling changes

20-241/S-025 & 20-764/S-018; submitted 6/29/04-Proposes several labeling changes, and presents the results of drug-interaction studies

20-241/S-026 & 20-764/S-019; submitted 8/20/04-Revises the patient package insert (PPI)

These applications have been reviewed by Dr. Philip Sheridan, medical officer; Dr. Kun He, statistician; Dr. Andre Jackson, Office of Clinical Pharmacology and Biopharmaceutics; and Dr. John Feeney, Neurology Drugs Team Leader. The review team recommends that the applications be considered approvable. I will present the relevant data very briefly, and offer the rationale for the division's action.

Effectiveness and Safety

As noted, the sponsor has presented the results of a single randomized placebo controlled trial in patients ages 2-adult receiving Lamictal as adjunctive therapy for the treatment of primarily generalized tonic-clonic seizures. As the clinical/statistical team notes, there is clear evidence of effectiveness of Lamictal in this setting. I have only a few comments.

First, the number of patients being treated with concomitant non-EIAEDs is quite small (about 10% of the total study sample received at least one such drug). The number of patients treated with any given non-EIAED was extremely small, except for topiramate (N=12). To the extent that this study was, in part, intended to provide empirical evidence that Lamictal is effective when given with these drugs, or to generate meaningful plasma level data in these patients, it must be concluded that the evidence is weak, given the small numbers (see below for a discussion of the plasma level data). Nonetheless, the overall result is quite robust.

Further, as noted by Dr. Feeney, the estimate of the treatment effect in the 2-5 year old group actually favors placebo. The most extreme worsening on Lamictal in the entire study was seen in a patient in this group, and an analysis with this patient removed still favors placebo. It should be noted that the placebo response in this sub-group is quite high (71% median reduction in seizures, compared to an overall placebo response of about a 34% reduction). My view is that this discrepant drug-placebo difference in this younger age group is likely a chance finding, perhaps related to the unusually high placebo response rate in this group and the post-hoc nature of the sub-grouping. There is no obvious pharmacokinetic reason for a lack of response in this group, and the fact that we have previously concluded that Lamictal is effective down to the age of 2 years in the treatment of the generalized seizures of Lennox-Gastaut syndrome support, in my view, granting a claim for PGTC seizures down to this age as well.

There were no important safety issues.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Oral Contraceptives (OCs)

Patients treated with OCs have significantly decreased Lamictal plasma levels. However, during the week of the cycle in which no active OC is given, Lamictal levels increase, so that by the end of that week, Lamictal plasma levels are on average about twice those that obtain during the rest of the cycle in which active OCs are administered. As Dr. Feeney notes, this could give rise to unacceptable adverse events, especially if the patient is being treated with a maximally tolerated Lamictal dose during the active phase of OC treatment.

Further, the sponsor proposes labeling that suggests that patients being treated with Lamictal and concomitant oral contraceptives (OCs) who are not also taking enzyme-inducing AEDs may need to be treated with a dose of Lamictal that is twice "the recommended target maintenance dose,". However, this may give rise to clinical scenarios for which we have little to no experience. For example, in patients being treated with a non-enzyme inducing AED, this could result in a daily dose of 750 mg. Further, in the conversion to monotherapy regimen the sponsor proposes, this could result in a daily dose of Lamictal (as pre-monotherapy combination treatment) of up to 1000 mg (see below). Although I understand the pharmacokinetic basis for this proposal, I have concerns about the tolerability of these doses. Indeed, in the conversion to monotherapy setting, the sponsor has not provided dosing recommendations to inform the prescriber how to lower a dose of Lamictal 1000 mg/day (or other doses between 1000 mg/day and 500 mg/day) to the recommended daily dose of 500 mg. Further, during the "pill-free" week of the cycle, such large doses would be expected to reach dangerously high plasma levels of Lamictal. These issues will need to be

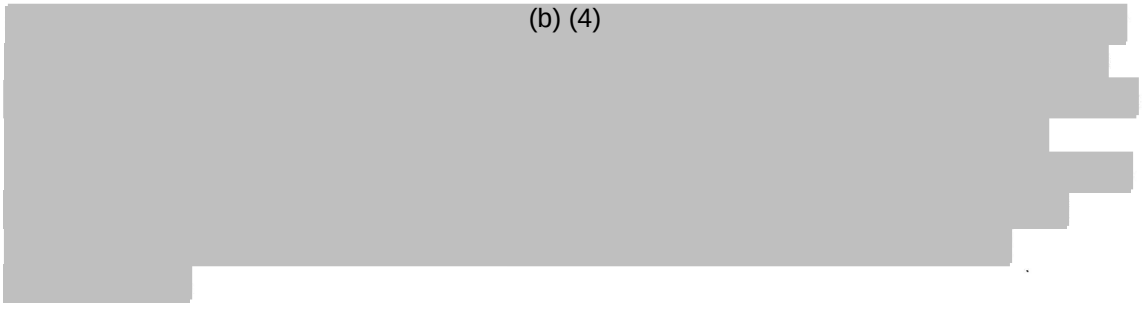
adequately addressed before we can write adequate directions for the concomitant use of Lamictal and OCs.

In addition, assuming these issues can be resolved, the cyclical increase in plasma levels of Lamictal that occur during the (latter part of) the "pill-free" week (even at more modest doses than those discussed above) may be associated with unacceptable adverse events in some patients. For this reason, as noted by Dr. Feeney, this phenomenon must be described more prominently in product labeling than is currently proposed.

Other issues are also problematic.

(b) (4)

(b) (4)



Other labeling proposals are also potentially problematic.

The sponsor has proposed, in numerous sections of labeling, to replace the phrase "enzyme-inducing AEDs" with the specific list of such AEDs (as well as rifampin). Although I have no objection to this specific substitution in most sections of the label, there are several concerns that the sponsor should address.

This substitution is inappropriate in those sections of labeling pertaining to dosing in patients with Bipolar Disorder. In these patients, most of the specific AEDs named are not relevant. Further, (b) (4)

(b) (4)

Removing the "enzyme-inducing" drugs language may be problematic in this regard.

Further, apropos the comments above related to the concomitant use of Lamictal and OCs, it might be reasonable to conclude that any drug with enzyme-inducing potency similar to that of the OCs should have the same dosing recommendations. However, as we have seen above, such recommendations may be problematic under certain circumstances, and these issues should be addressed.

Finally, Lamictal is apparently inactivated via glucuronidation by the UDP-glucuronyl-transferase system. Presumably, then, drugs that induce Lamictal metabolism do so by inducing this enzyme system. However, the average prescriber would likely not interpret the phrase "enzyme-inducing drug" as referring to an inducer of the UDP-glucuronyl-transferase system (more likely, prescribers would interpret this phrase as pertaining to the CYP450 enzyme system). Therefore, the sponsor should explicitly refer to the specific system induced when using the "enzyme-inducing drug" language in product labeling.

For the reasons given above, then, I have issued an Approvable letter, with appended draft labeling.

Russell Katz, M.D.

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/s/

Russell Katz
12/8/2005 08:50:29 AM
MEDICAL OFFICER

MEMORANDUM

NDA 20-241/S-027 and (b) (4) Lamictal (lamotrigine) Tablets
NDA 20-764/S-020 and (b) (4) Lamictal (lamotrigine) Chewable Dispersible Tablets

FROM: John Feeney, M.D.
Neurology Team Leader

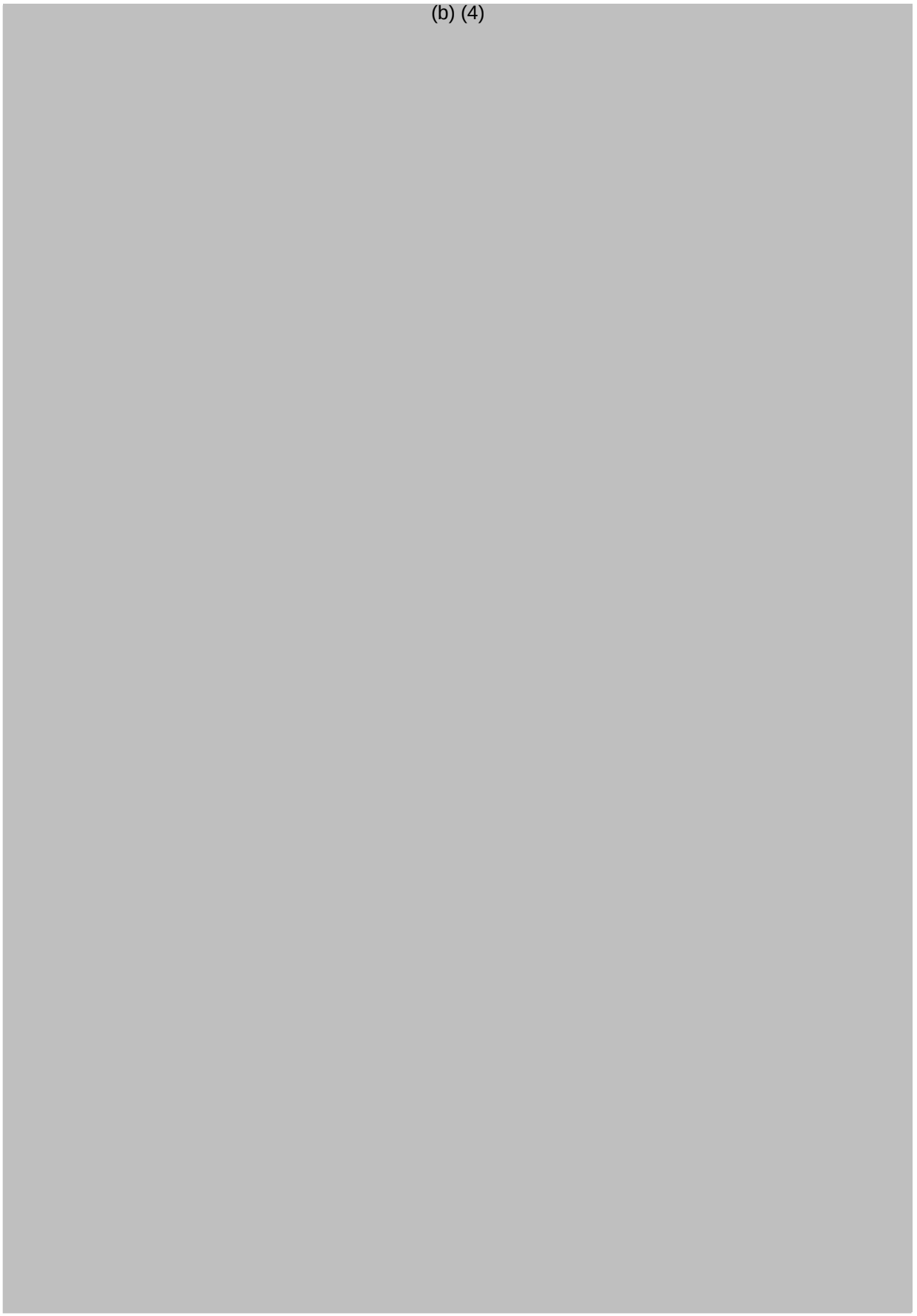
SUBJECT: (b) (4)

3. New Indication for Adjunctive Therapy in Primary Generalized Tonic-Clonic Seizures in Adult and Pediatric Patients
4. Miscellaneous Other CBE Supplements Dealing Primarily with Drug-Drug Interactions

DATE: December 5, 2005

(b) (4)

(b) (4)



2 Page(s) Withheld

___X___ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

_____ Law Enforcement Action (b7)

Adjunctive Therapy in Primary Generalized Tonic-Clonic Seizures

In support of this new indication, the sponsor conducted a single controlled trial enrolling both adult and pediatric patients. The clinical reviewer, Dr.Sheridan, and the statistical reviewer, Dr.Kun He, have both reviewed this trial in separate reviews.

LAM40097 was a randomized, double-blind, placebo-controlled parallel-group study. There was an 8 week baseline phase, a dose-escalation phase that varied in length depending on age, and a 12 week maintenance phase. Patients 2 years of age and older were enrolled who had at least 3 PGTC seizures during the 8 week baseline phase. Patients could be taking 1-2 concomitant AEDs.

Patients were dosed based on concomitant AEDs. There were 3 groups: those on EIAEDs, those on VPA, and those on concurrent AEDs other than the above. Dosing was different for ages 2-12 and those over the age of 12 years.

The primary efficacy outcome was the percent change from baseline in average monthly seizure frequency.

A total of 117 subjects were randomized, 58 to Lamictal and 59 to placebo. Roughly 45% of patients were on concurrent VPA and 45% were on concurrent EIAEDs. Roughly 10% of patients were on other AEDs (see p37 of Dr.Jackson's review for a complete list of these).

For the ITT population, the median percent change from baseline was -66% in the Lamictal group and -34% in the placebo group (p=0.006).

The results for median percent seizure reduction in the lower age groups are shown below:

Age	Lamictal	Placebo
2-5 years (n=9)	9	-71
6-12 years (n=14)	-84	-30

The results in the 2-5 year stratum were due in large part to one outlier, but even removing that outlier, the results trended in favor of placebo.

Safety

Dr.Sheridan has reviewed the safety data from this trial. No new safety issues have been identified. Dr.Sheridan believes the profile of the safety data from this trial mirrors the profile already reflected in current labeling. For this reason, Dr.Sheridan and the sponsor do not wish to alter the Adverse Events section of current labeling. This seems reasonable.

Miscellaneous Labeling Supplements

NDA 20-241/S-010
NDA 20-764/S-003

These supplements were originally submitted in February 1999; an Approvable Letter was sent in December 2002. The sponsor proposed changes to 4 sections of labeling:
1. Patients with Hepatic Impairment/Precautions and Dosage and Administration
2. Hypersensitivity Reactions/Warnings
3. Acute Multiorgan Failure/Warnings
4. Overdosage

In the Approvable Letter, the division agreed with the changes to 2-4 above, but proposed specific alternative language to the hepatic impairment sections.

NDA 20-241/S-021
NDA 20-764/S-014

These supplements were originally submitted in May 2003 and amended in August 2004. The sponsor proposed changes in 4 areas:
1. To add a description of the effect of lamotrigine on kindling to the Mechanism of Action section
2. Drug-drug interaction with oral contraceptives
3. Information on re-starting Lamictal and re-titration of Lamictal after brief interruptions in therapy
4. Information on lamotrigine levels during pregnancy

The pharm/tox reviewer, Dr.Fisher agrees with the first addition. Changes 3 and 4 are also acceptable.

The proposed language for the interaction with oral contraceptives is found in the Precautions section and the Dosage and Administration section. Oral contraceptives induce the metabolism of lamotrigine resulting in a 50% reduction in circulating levels. Therefore, higher doses of lamotrigine may be needed with the 2-drug combination. Additionally, when the active component of oral contraceptives is held for 1 week of the 4 week cycle, plasma levels of lamotrigine will gradually increase over the course of the week, doubling on average by the end of the week. This latter point is described in the Drug-Drug Interactions/Precautions section of proposed labeling, but not in the Dosage and Administration section.

I believe this latter doubling of plasma lamotrigine levels during the 28-day cycle on oral contraceptives needs to be more prominently highlighted in labeling. Given the excess in adverse events that could accrue (even if for only 1-2 days),

this seems like information that should be more obvious for the patients and prescribers alike.

NDA 20-241/S-025
NDA 20-764/S-018

These supplements were submitted in June 2004. They proposed removing the terminology EIAEDs from the label, substituting the actual drugs, phenytoin, primidone, phenobarbital, and carbamazepine. Additions to labeling describing drug-drug interactions were also proposed for:
1. Rifampin
2. Trileptal
3. Keppra
4. Olanzapine

These changes are acceptable.

NDA 20-241/S-026
NDA 20-764/S-019

These supplements were submitted in August 2004. They propose changes to the Patient Information Leaflet in keeping **with the division's recommendations** aimed at reducing confusion between Lamictal and other drugs, especially Lamisil, in the marketplace due to name confusion.

These changes are acceptable.

Conclusions

The sponsor *has* provided evidence for the effectiveness of Lamictal in the treatment of generalized tonic-clonic seizures for patients 6 years of age and above. Very few patients below the age of 6 years were enrolled and, for those patients, the results trended in favor of placebo.

(b) (4)

The sponsor *has not* provided adequate information to support (b) (4)

(b) (4)

The current applications and the miscellaneous labeling supplements described above have provided information on a number of drug-drug interactions that the sponsor has not described in their proposed labeling. The sponsor should be asked to update labeling with this information.

The particular interaction between lamotrigine and oral contraceptives seems to warrant more prominent labeling. In particular, the doubling of plasma lamotrigine levels in a cyclical fashion with concomitant oral contraceptives could be problematic for many patients. Prescribers may wish to consider this fact in choosing which AED to prescribe with concomitant oral contraceptives. The sponsor should be asked to address this issue further.

Recommendations

The sponsor should be sent an Approvable Letter with draft labeling. Labeling should ultimately:

1. Reflect that the new indication is only for patients 6 years of age and older;
2. Highlight the oral contraceptive drug interaction, especially the cyclical doubling of lamotrigine levels;
3. Include results of drug-drug interaction studies;
4. Accurately describe use in hepatically impaired patients.
5. (b) (4)

6. The sponsor should be asked to further study the interaction of Lamictal with gabapentin, pregabalin, and tiagabine. They should also be asked to provide drug-drug interaction data on any future AEDs approved in the U.S.
7 (b) (4)

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/s/

John Feeney
12/5/2005 01:51:47 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-241/S-027 and 20-764/S-020

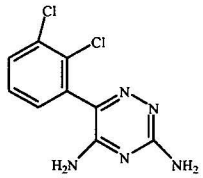
CHEMISTRY REVIEW(S)

CHEMIST REVIEW
OF **SUPPLEMENT**

1. **ORGANIZATION:** HFD-120
2. **NDA NUMBER:** **20-241 & 20-764**
4. **SUPPLEMENT NUMBERS/DATES:** SE1-027 & SE1-020
   letterdate: 4-FEB-2005
   stampdate: 7-FEB-2005
5. **AMMENDMENTS/REPORTS/DATES:** 31-AUG-2005
6. **RECEIVED BY CHEMIST:** 14-FEB-2005

7. **APPLICANT NAME AND ADDRESS:** SmithKline Beecham Corporation d/b/a GlaxoSmithKline
   One Franklin Plaza
   P.O. Box 7929
   Philadelphia, PA 19101

8. **NAME OF DRUG:** Lamictal®
9. **NONPROPRIETARY NAME:** lamotrigine
10. **CHEMICAL NAME/STRUCTURE:** 6-(2,3-dichlorophenyl)-1,2,4-Triazine-3,5-diamine



CAS registry # [84057-84-1]

11. **DOSAGE FORM(S):** Tablets (20-241)
    Chewable Dispersible Tablets (20-764)

12. **POTENCY:** Tablets: 25, 50, 100, 150, 200 & 250 mg
    Chewable: 2, 5, 25, 100 mg

13. **PHARMACOLOGICAL CATEGORY** Antiepileptic

14. **HOW DISPENSED:** XXX (RX) ___ (OTC)
15. **RECORDS & REPORTS CURRENT:** XXX (YES) ___ (NO)
    SPECIAL PRODUCTS ___ (YES) XXX (NO)
16. **RELATED IND/NDA/DMF:**

17. **SUPPLEMENT PROVIDES FOR:** approval of Lamictal as adjunctive treatment of primary generalized tonic-clonic seizures in pediatric and adult patients. (b) (4)

18. **COMMENTS:** Approval of this application has the potential to increase it use, therefore an Environmental Assessment (EA) was included. The EA was evaluated by Dr Florian Zielinski, and a finding of no significant impact (FONSI) was determined on 8 APR 2005. No other CMC- related changes are proposed.

19. **CONCLUSIONS AND RECOMMENDATIONS:** Recommend approval of these applications from a CMC perspective. Overall approval will require clinical concurrence.

20. **REVIEWER NAME**	**SIGNATURE**	**DATE COMPLETED**
David J. Claffey, Ph.D.	_____	14 NOV 2005

cc: Orig. NDA 20-241, 20-764
HFD-120/CCalder
HFD-810/DClaffey
HFD-810/ MHeimann

filename: N 20-241(S-027) & 20-764(S-020) lamictal.doc

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/s/

David Claffey
11/29/2005 10:12:56 AM
CHEMIST

Martha Heimann
11/29/2005 10:24:34 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-241/S-027 and 20-764/S-020

ENVIRONMENTAL ASSESSMENT

FONSI AND

ENVIRONMENTAL ASSESSMENT

FOR

LAMICTAL (lamotrigine) Tablets
NDA 20-241 / S-027

and

LAMICTAL (lamotrigine) Chewable Dispersible Tablets
NDA 20-764 / S-020

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurological Drug Products
(HFD-120)

Date Completed: April 8, 2005

FINDING OF NO SIGNIFICANT IMPACT

LAMICTAL (lamotrigine) Tablets NDA 20-241 / S-027 and
LAMICTAL (lamotrigine) Chewable Dispersible Tablets NDA 20-764 / S-020

(Treating patients with primary generalized tonic-clonic seizures)

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement, therefore, will not be prepared.

In support of its supplemental new drug applications, GlaxoSmithKline prepared an environmental assessment (attached) in accordance with 21 CFR Part 25 (b) that evaluates the potential environmental impacts of the use and disposal from use of the products. The supplements request approval of Lamictal (lamotrigine) Tablets (NDA 20-241 / S-027) and Lamictal (lamotrigine) Chewable Dispersible Tablets (NDA 20-764 / S-020) for treating patients with primary generalized tonic-clonic seizures.

Lamictal Tablets contain lamotrigine, a synthetic drug substance that will enter the environment from patient use and disposal. Therefore, its toxicity to environmental organisms was characterized. The results indicate that it is not expected to be toxic to aquatic organisms at expected environmental concentrations.

In U.S. hospitals and clinics, empty or partially empty packages will be disposed of according to hospital/clinic procedures. When used in the home, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of the unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

April 8, 2005
DATE

PREPARED BY
Florian Zielinski
Environmental Officer
Center for Drug Evaluation and Research

DATE

CONCURRED BY
Jon E Clark
Associate Director for Policy
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

DATE

CONCURRED BY
Moheb M Nasr
Acting Director, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Attachment: Environmental Assessment
Appended Electronic Signature Page

1. Date

December 20, 2004

2. Name of Applicant

SmitkKline Beecham Corporation d/b/a GlaxoSmithKline

3. Address

P.O. Box 7929
One Franklin Plaza
Philadelphia PA, 19101

4. Description of Proposed Action

4.1 Requested Approval

GlaxoSmithKline requests approval to manufacture and market Lamictal tablets for the control of primary generalized tonic-clonic seizures.

A full Environmental Assessment (EA) was previously submitted for Lamictal 100, 150, 200 and 250 mg tablets (NDA 20 – 241).

4.2 Need for Action

Lamictal (lamotrigine) is an antiepileptic drug (AED) of the phenyltriazine class, and is chemically unrelated to existing AEDs. It has been approved in combination with other AEDs (called adjunctive therapy) by the U.S. Food and Drug Administration (FDA), as well as for stand-alone medication (also called "monotherapy") for adults. In placebo controlled clinical studies it has been shown to be very well tolerated and it is highly effective in reducing seizure frequency in patients with partial seizures including secondarily generalized seizures.

The requested approval will allow the product to be marketed for the treatment of patients with primary generalized tonic-clonic seizures.

4.3 Locations of Use

Lamictal will be used in the United States of America, with predominant use coinciding with areas of greatest population density.

4.4 Disposal Sites

At hospitals, pharmacies, and clinics, empty or partially empty packages will be disposed of in accordance with hospital, pharmacy, or clinic procedures. In homes, empty or partially empty packages will be disposed of by the community's solid waste management system; which may include landfills, incineration, and recycling. Minimal quantities of unused drug product may be disposed of in the sanitary sewer system.

5. Identification of Substances that are the Subject of the Proposed Action

5.1 Nomenclature

Lamictal contains the active moiety (API) lamotrigine. The environmental studies reported herein were conducted with lamotrigine.

United States Adopted Name (USAN): lamotrigine

Chemical Name: 3,5-diamino-6-(2,3-dichlorophenyl)-as-triazine

5.2 Chemical Abstracts Service (CAS) registration number

CAS Number: 84057-84-1

5.3 Molecular Formula

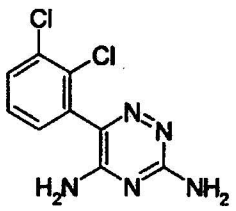
Molecular Formula: $C_9H_7N_5Cl_2$

5.4 Molecular Weight

Molecular Weight: 256.1

5.5 Structural Formula

Structural formula:



6. Environmental Issues

Details regarding the environmental fate and effects of lamotrigine are detailed in previously submitted Environmental Assessment information [1] [2]. Additional physico-chemical data have recently been obtained and pertinent results are summarized below [7] [8].

6.1 Physical and Chemical Characteristics

Physico-chemical properties for lamotrigine are found in Table 1.

Table 1. Physical and Chemical Properties of Lamotrigine

pKa dissociation constant	5.7
Vapour Pressure (Clausius-Clapeyron equation)	3×10^{-8} torr
Water solubility	0.17 mg/mL @ 25°C
Hydrolysis	Hydrolysis rate < 10^{-5}/sec < 10% @50°C for 1 week
Log P (0.001M)	< 1 at pH 5 1.4 at pH 7 1.4 at pH 9
Modified Sturm Test	0% in 28 days Not Readily Biodegradable
Inherent Biodegradability	0% in 14 days Not Inherently Biodegradable
Absorption onto Activated Sludge	K = 14, compound unlikely to absorb to sludge.

Lamotrigine has a relatively low water solubility (0.17 mg/mL) but nonetheless is likely to amass predominantly in the aquatic compartment. A low distribution coefficient of 14 for the sludge sorption study suggests that the substance is unlikely to adsorb to sludge [8]. The vapour pressure estimate is less than 10^{-7} torr and therefore lamotrigine is not expected to affect the atmospheric compartment [1]. The measured logP value is less than 3 and

consequently lamotrigine is not expected to bioaccumulate or sorb onto organic substances. The terrestrial compartment is unlikely to be directly affected.

6.2 Environmental Depletion Mechanisms

Various depletion mechanisms, including hydrolysis, inherent and aerobic biodegradation, have been investigated for lamotrigine [1] [2] [7].

Hydrolysis: Lamotrigine is hydrolytically stable with a half-life greater than 1 year at 25°C. Hydrolysis is not considered to be a primary removal process.

Aerobic degradation in water: Lamotrigine does not classify as readily biodegradable under the conditions of the test (Biodegradation in water, USFDA; Modified Sturm test, OECD guideline 301B).

Inherent Biodegradability: Lamotrigine does not classify as inherently biodegradable under the conditions of the test (Biodegradation Zahn-Wellens/EMPA test, OECD guideline 302B).

Photolysis (UV spectra): The spectrum of lamotrigine shows a considerable red shift with the maximum changing from 260nm in acid media to near 300nm at a pH of 6 or above indicating that lamotrigine may undergo photodegradation [1].

Lamotrigine is unlikely to be removed from the environment via hydrolysis or biodegradation although exposure to UV light may present itself as a means of removal.

6.3 Environmental Concentrations

Five year forecasts of expected production volumes of lamotrigine have been revised as a result of this new indication and the calculated expected introductory concentration is greater than 1 part per billion threshold, see Confidential Appendix A. Based upon dilution factors for publicly owned treatment works (POTWs) available from the EPA, applying a dilution factor of 10 to the EIC-aquatic to estimate the expected environmental concentration (EEC) is appropriate [3]. However, as Lamotrigine is expected to persist in the environment, the EIC conservatively will be considered equal to the maximum expected environmental concentration (MEEC).

6.4 Aquatic Ecotoxicity

Results of aquatic testing are summarized in Table 2. Details regarding the environmental fate and effects of lamotrigine are detailed in previously submitted Environmental Assessment information [1] [2].

Lamotrigine has had no inhibitory effect on the microorganisms tested and therefore is not expected to adversely affect local wastewater treatment plants [1] [2]. Additional aquatic toxicity data has recently been obtained and pertinent results are summarized below in Table 2, [4] [5] [6]. Aquatic testing had been performed to the level of *Tier 2* including the base set of aquatic organisms of (1) Acute toxicity to Daphnia (2) Acute Toxicity to algae (3) Acute Toxicity to Fish. Based on the lowest NOEC value for the most sensitive organism in the base set, and revised MEEC value, the calculated assessment factor for Lamotrigine is much greater than the maximum assessment factor of 100 cited in the FDA Environmental Assessment Document [3] and therefore no further testing need be conducted, see Confidential Appendix B.

Table 2. Aquatic Toxicity Data for Lamictal.

TEST	EC50 (mg/L)	NOEC (mg/L)
Activate Sludge Respiration Inhibition Test (ASRIT)	IC50 > 1000	1000
Microbial Inhibition Test	> 185	185
Acute Toxicity to Daphnia magna	56 (48 hours)	30 (48 hours)
Toxicity to Green Alga Selenastrum capricornutum	39.7 (72 hours)	7.5 (72 hours)
Acute Toxicity to Rainbow Trout Oncorhynchus mykiss	85 (96 hours)	60 (96 hours)

6.5 Summary

Lamotrigine will amass predominantly in the aquatic environment. For the most sensitive species, the NOEC/EIC ratios were much greater than the minimum assessment factor (AF) of 100 given for tier 2 ecotox data in the FDA Guidance Document [3]. It can be concluded that the clinical use of lamotrigine at predicted production levels will not cause adverse effects to the environment.

7. Mitigation Measures

No potentially adverse environmental impacts have been identified for the proposed action. Therefore, no mitigation measures are proposed.

8. Alternatives to the Proposed Action

No potentially adverse environmental impacts have been identified for the proposed action. The only alternative to the proposed action is that of no action, thus depriving patients of an important therapy. The approval of Lamictal (lamotrigine) will provide an important benefit to patients requiring its administration with no known adverse environmental risk.

9. List of Preparers

Jim Ryan
Senior Scientist, Environmental Process Design, Chemical Development, GlaxoSmithKline, UK.

PhD in Molecular Biology, Imperial College, London, 1998.

Contributors:
Scott Ziegenfuss
Manager, Global CMC Regulatory Affairs, RA, GlaxoSmithKline, US

Robert Hannah
Director, Environment Hazard Assessment, GlaxoSmithKline, US.

10. References

1. NDA 20-241, Environmental Assessment Information for Lamictal 100,150,200 and 250 mg Tablets, Burroughs Wellcome Co., 3030 Cornwallis Road, Research Triangle Park, NC 27709, Submitted to FDA in NDA 20-241.

2. NDA 20-241, Supplemental Environmental Assessment Information for Lamictal (Lamotrigine) Dispersible /Chewable tablets, Burroughs Wellcome Co., 3030 Cornwallis Road, Research Triangle Park, NC 27709 March 31 1995.

3. FDA, 1998, Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications, US FDA CDER, CMC 6, revision 1, July 1998.

4. Brixham Environmental Laboratory, Zeneca, Ltd. Lamotrigine: Determination of Acute Toxicity to Daphnia magna. Brixham Study 03-0200/B. March 2004.

5. Brixham Environmental Laboratory, Zeneca, Ltd. Lamotrigine: Determination of Toxicity to the green algae Selenastrum capricornutum. Brixham Study 03-0200/C. March 2004.

6. Brixham Environmental Laboratory, Zeneca, Ltd. Lamotrigine: Determination of Acute Toxicity to Rainbow Trout (Oncorhynchus mykiss). Brixham Study 03-0200/D. March 2004.

7. Brixham Environmental Laboratory, Zeneca, Ltd. Lamotrigine: Determination of Inherent Biodegradability (Zahn-Wellens test). Brixham Study 03-0200/E. March 2004.

8. Brixham Environmental Laboratory, Zeneca, Ltd. Lamotrigine: Determination of Adsorption onto activated sludge. Brixham Study 03-0200/f. March 2004.

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/s/

Jon E. Clark
5/5/05 09:59:06 AM

Moheb Nasr
5/6/05 08:11:53 AM

REVIEW OF

ENVIRONMENTAL ASSESSMENT

FOR

LAMICTAL (lamotrigine) Tablets
NDA 20-241 / S-027

and

LAMICTAL (lamotrigine) Chewable Dispersible Tablets
NDA 20-764 / S-020

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurological Drug Products
(HFD-120)

Date Completed: April 8, 2005

EXECUTIVE SUMMARY:

FONSI recommended.

FONSIs were approved in 1997 for Lamictal (lamotrigine) Tablets (NDA 20-241) and Lamictal (lamotrigine) Chewable Dispersible Tablets (NDA 20-764). "Categorical exclusion from the requirement to prepare an Environmental Assessment" based on $EIC_{(aq)}$ less than 1 ppb was not available at that time.

Lamotrigine is an antiepileptic drug for treating adults with epilepsy. The Supplements request approval for treatment of primary generalized tonic-clonic seizures. The maximum annual production estimate (b) (4) kg) for lamotrigine corresponds to $EIC_{(aq)}$ = (b) (4) ppb in any of the next 5 years after approval of the supplements.

Lamotrigine is not volatile and will not enter the air compartment. Lamotrigine hydrolysis is less than 10% per week in water at 50°C; its hydrolysis half-life is greater than 1 year at 25°C. Lamotrigine is not readily biodegradable (Aerobic Degradation in Water, OECD 301 B). Lamotrigine is not inherently biodegradable (OECD 302 B). Lamotrigine is not expected to absorb to sludge (K = 14). Its log octanol water partition coefficient is 1.4 at pH 7 to 9 and < 1 at pH 5. As a result, lamotrigine is not expected to bioaccumulate or sorb onto soil. Lamotrigine absorbs UV at 300 nm at pH 6 indicating some potential photodegradation. Lamotrigine has relatively low solubility in water (0.17 mg/L at 25°C) but it is expected to enter the aquatic environment through effluents discharged by publicly owned treatment works (POTW). The Expected Introduction Concentration ($EIC_{aquatic}$) is (b) (4) ppb assuming no metabolism, no hydrolysis and no photolysis. The Predicted Environmental Concentration (PEC) in the aquatic environment is (b) (4) ppb. The PEC was calculated using a dilution factor of 10 for wastewater effluents discharged into the receiving waters.

Environmental effect data were generated for aquatic species. It is unlikely that lamotrigine represents a risk to the aquatic environment based on the available data.

Lamotrigine Effects, Testing Data		
Activated Sludge Respiration Inhibition Test: IC_{50} > 1 g/L; NOEC = 1 g/L		
Microbial Inhibition	EC_{50} > 185 mg/L	NOEC = 185 mg/L
Daphnia, acute, 48 hr	EC_{50} = 56 mg/L	NOEC = 30 mg/L
Green alga, 72 hr	EC_{50} = 39.7 mg/L	NOEC = 7.5 mg/L
Rainbow Trout, 96 hr	LC_{50} = 85 mg/L	NOEC = 60 mg/L

Summary: No significant environmental impact is anticipated based on the data submitted.

REVIEW of ENVIRONMENTAL ASSESSMENT

1. **Date:** EA dated December 20,2004
   Project Mgr: Courtney R Calder (301) 594-5528

2. **Name of applicant/petitioner:** GlaxoSmithKline

   ADEQUATE

3. **Address:** PO Box 7929, One Franklin Plaza, Philadelphia, PA 19101

   ADEQUATE

4. **Description of the proposed action:**

   a. **Requested Approvals (NDA 20-241 / S-027 and NDA 20-764 / S-020):**

   GlaxoSmithKline filed Supplements pursuant to section 505(b) of the Federal, Food, Drug & Cosmetic Act for Lamictal (lamotrigine) Tablets (25, 50, 100, 150, 200 and 250 mg, NDA 20-241 / S-027) and Lamictal (lamotrigine) Chewable Dispersible Tablets (5, 25 and 100 mg, NDA 20-764 / S-020).

   Lamotrigine is an antiepileptic drug for monotherapy and adjunctive therapy of partial seizures in adults with epilepsy. The supplements request approval of lamotrigine for treating patients with primary generalized tonic-clonic seizures.

   ADEQUATE

   b. **Need for Action:**

   The supplements request approval of lamotrigine for treating patients with primary generalized tonic-clonic seizures.

   ADEQUATE

   c. **Expected Locations of Use (Drug Product):**

   Lamotrigine will be used throughout the USA.

   ADEQUATE

d. Disposal Sites

Hospitals, pharmacies and clinics will dispose of empty or partially empty packages in accordance with their waste handling procedures. When used in the home, empty or partially empty packages containing lamotrigine will be disposed of by a **community's solid waste management system, which may include landfills,** incineration and recycling. Minimal quantities of unused drug may be disposed of in the sewer system.

ADEQUATE

5. **Identification of the chemical that is the subject of the proposed action:**

a. Nomenclature
   i. Established Name (USAN): lamotrigine
   ii. Trade Name: Lamictal
   iii. Chemical name: 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine
b. CAS Registration Number: 84057-84-1
c. Molecular Formula: $C_9H_7N_5Cl_2$
d. Molecular Weight: 256.1
e. Chemical Structure is in Section 5.5 of the EA, page 7

ADEQUATE

6. Environmental Issues:

FONSIs were approved in 1997 for Lamictal (lamotrigine) Tablets (NDA 20-241) and Lamictal (lamotrigine) Chewable Dispersible Tablets (NDA 20-764). "**Categorical** exclusion from the **requirement to prepare an Environmental Assessment" based on** $EIC_{(aq)}$ less than 1 ppb was not available at that time.

Lamotrigine is an antiepileptic drug for treating adults with epilepsy. The Supplements request approval of lamotrigine for treatment of primary generalized tonic-clonic seizures. The maximum annual production estimate ((b) (4) kg) for lamotrigine corresponds to $EIC_{(aq)}$ = (b) (4) ppb in any of the next 5 years after approval of the supplements.

The EA contains physiochemical, fate and effects data for lamotrigine and refers to test reports submitted earlier. Testing procedures to support the approval of the supplements were done according to EPA, FDA EA-TAH or OECD Guidelines.

Environmental Fate of Released Substances

i. Identification of Substances of Interest

Lamotrigine is the active ingredient in Lamictal Tablets and Lamictal Chewable Dispersible Tablets.

ADEQUATE

ii. Physical and Chemical Characterization

Lamotrigine is not volatile and will not enter the air compartment.

Lamotrigine hydrolysis is less than 10% per week in water at 50°C; its hydrolysis half-life is greater than 1 year at 25°C.

Lamotrigine is not readily biodegradable (Aerobic Degradation in Water, OECD 301 B).

Lamotrigine is not inherently biodegradable (OECD 302 B).

Lamotrigine is not expected to absorb to sludge (K = 14).

Its log octanol water partition coefficient is 1.4 at pH 7 to 9 and < 1 at pH 5. As a result, lamotrigine is not expected to bioaccumulate or sorb onto soil.

Lamotrigine absorbs UV at 300 nm at pH 6 indicating some potential photodegradation.

Lamotrigine has relatively low solubility in water (0.17 mg/L at 25°C) but it is expected to enter the aquatic environment through effluents discharged by publicly owned treatment works (POTW).

ADEQUATE

iii. Environmental Depletion Mechanisms

Lamotrigine absorbs UV at 300 nm at pH 6 indicating some potential photodegradation.

ADEQUATE

iv. Environmental Concentration, aquatic

The Expected Introduction Concentration ($EIC_{aquatic}$) is (b) (4) ppb assuming no metabolism, no hydrolysis and no photolysis. The Predicted Environmental Concentration (PEC) in the aquatic environment is (b) (4) ppb. The PEC was calculated using a dilution factor of 10 for wastewater effluents discharged into the receiving waters.

ADEQUATE

v. Summary

Lamotrigine will enter the aquatic environment through effluents discharged by publicly owned treatment works (POTW). Lamotrigine is not volatile and therefore will not enter the air compartment. Lamotrigine is expected to be persistent in the environment due to its minimal potential for photolysis.

ADEQUATE

Environmental Effects of Lamotrigine

Environmental effect data were generated for aquatic species. It is unlikely that lamotrigine represents a risk to the aquatic environment based on the available data.

Lamotrigine Effects, Testing Data		
Activated Sludge Respiration Inhibition Test: IC_{50} > 1 g/L; NOEC = 1 g/L		
Microbial Inhibition	EC_{50} > 185 mg/L	NOEC = 185 mg/L
Daphnia, acute, 48 hr	EC_{50} = 56 mg/L	NOEC = 30 mg/L
Green alga, 72 hr	EC_{50} = 39.7 mg/L	NOEC = 7.5 mg/L
Rainbow Trout, 96 hr	LC_{50} = 85 mg/L	NOEC = 60 mg/L

Summary of Lamotrigine Effects Data

The introduction of the lamotrigine into sewage treatment plants and into the environment through use and disposal of the product is not expected to pose an environmental risk.

Based on the Microbial Inhibition Test, lamotrigine does not inhibit the growth of microbial strains or species at concentrations expected in wastewater treatment plants. Therefore it is not expected to disrupt the ecosystem.

The applicant performed acute toxicity testing with *daphnia magna*. The 48 hour EC_{50} = 56 mg/L, the NOEC measured is 30 mg/L. The EC_{50} to EIC ratio is greater than 30,000. The NOEC is more than 20,000 times greater than the EIC, namely (b) (4) mg/L, indicating that no effects would be

expected.

The applicant performed acute toxicity testing with rainbow trout. The 96 hour EC_{50} = 85 mg/L, the NOEC measured is 60 mg/L. The EC_{50} to EIC ratio is greater than 50,000. The NOEC is more than 40,000 times greater than the EIC, namely (b) (4) mg/L, indicating that no effects would be expected.

ADEQUATE

Summary Evaluation: Based on the above data, a FONSI is recommended

7. Mitigation Measures

No adverse environmental effects have been identified.
No mitigation measures are required.

ADEQUATE

8. Alternatives to the proposed action

No potential effects have been identified for this proposed action.
No alternatives to the proposed action are required.

ADEQUATE

9. Preparers

The names and professional experience of the EA preparers are provided

ADEQUATE

10. References

Eight references are provided.

ADEQUATE

11. Appendices

The EA contains a two confidential Appendixes (A and B) that include calculations of EIC and EEC (expected no effect concentration) based on the maximum annual production estimate ((b) (4) kg) in any of the next 5 years.

ADEQUATE

12. Certification

Two executives of GlaxoSmithKline provide certification that the information in the submitted EA is true, accurate and complete on the Cover page.

ADEQUATE

Reviewed by Florian Zielinski, April 8, 2005

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/s/

Florian Zielinski
5/4/05 03:15:44 PM
ENV ASSESSMENT

Jon E. Clark
5/5/05 09:59:25 AM
CHEMIST

Moheb Nasr
5/6/05 08:12:30 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-241/S-027 and 20-764/S-020

STATISTICAL REVIEW(S)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCE
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Serial Number:	20-241/S-027 & 20-764/S-020
Drug Name:	Lamictal ® (lamotrigine)
Indication:	Seizure
Applicant:	GlaxoSmithKline
Date:	2/4/2005
Review Priority:	Standard
Biometrics Division:	I (HFD 710)
Statistical Reviewer:	Kun He
Concurring Reviewers:	Kun Jin, , Ph.D.,Team Leader Kooros Mahjoob, Ph.D., Deputy Director
Medical Division:	Neuropharmacological Drug Products (HFD 120)
Clinical Team:	Philip Sheridan, M.D., Clinical Reviewer John Feeney, M.D., Team Leader Russell Katz, M.D., Director
Project Manager:	Courtney Calder, R. Ph.

Keywords: PGTC seizure, ANOVA

TABLE OF CONTENTS

Statistical Review and Evaluation

1. Executive Summary

1.1 Conclusions and Recommendations

The data from Study LAM40097 provided evidence that there was a statistically significant difference in favor of lamotrigine (LTG) as adjunctive therapy for treatment of primary generalized tonic-clonic (PGTC) seizures in pediatric and adult patients, compared to placebo, for the median percent change in PGTC seizure frequency from baseline at the end in the ITT population.

1.2 Brief Overview of Clinical Studies

The information provided in the current application supports the efficacy and safety of LTG as adjunctive therapy for treatment of PGTC seizures in pediatric and adult patients. The application consists of a single pivotal study (LAM40097) to support this indication.

The primary objective of this study was to assess the efficacy of LTG adjunctive therapy in subjects with PGTC seizures. This was a double-blind, randomized, placebo-controlled, parallel-group, multicenter study. The study comprised a Screen and three phases: Baseline (8 weeks), Dose Escalation (12 weeks for subjects 2-12 years of age and 7 weeks for subjects >12 years of age), and Maintenance (12 weeks). Subjects attended the clinic for safety and efficacy evaluations at Baseline Weeks 4 and 8, and at Treatment Weeks 3, 7, 11, 15, and 19 (subjects >12 years of age) or Treatment Weeks 3, 7, 11, 15, 19, and 24 (subjects 2-12 years of age). A total of 117 subjects were randomized and received double-blind study drug (58 received LTG and 59 received matched placebo). There were total of 52 centers in this study: 45 in the USA, 4 in Argentina, 2 in Chile, and 1 in Peru.

1.3 Statistical Issues and Findings

The data and analyses from Study LAM40097 showed that there was a statistically significant difference in favor of LTG, compared to placebo, for the median percent change in PGTC seizure frequency from baseline at the end in the ITT population.

The median percent change in PGTC seizure frequency from baseline at the end in the ITT population was -66.47 with range -100.0 to 144.9 for 58 patients in LTG group, and -34.20 with range -100.0 to 430.6 for 59 patients in placebo group, respectively. The ANOVA based on ranks with treatment group and age category as predictor variables for analyzing the median percent change had p-value .006.

For patients between 2-16 years old, the median percent change in PGTC seizure frequency from baseline at the end in the ITT population was -72.94 with range -100.0 to 31.9 for 16 patients in LTG

group, and -42.23 with range -100.0 to 379.8 for 20 patients in placebo group, respectively.

For patients between 2-12 years old, the median percent change in PGTC seizure frequency from baseline at the end in the ITT population was -79.72 with range -100.0 to 31.9 for 12 patients in LTG group, and -43.47 with range -100.0 to 379.8 for 11 patients in placebo group, respectively.

Since the sample size calculation is not based on the analytical comparisons for the lower age groups of 2-12 and 2-16, statistical tests based on ANOVA are not significant for the lower age groups. Although LTG is numerically better than placebo in the lower age groups, it is hard to judge whether the evidence is convincing due to few subjects in the lower age groups.

2. Introduction

2.1 Overview

LAMICTAL™ is an anti-epileptic drug that is chemically unrelated to other currently marketed anti-epileptic drugs. The anti-convulsant effects of lamotrigine (LTG) may result from its ability to block presynaptic voltage sensitive sodium channels, thereby stabilizing neuronal membranes and inhibiting the release of excitatory amino acid neurotransmitters (e.g., glutamate and aspartate) that play a role in the generation and spread of epileptic seizures. LTG is currently licensed in over 90 countries for add-on treatment of partial seizures in adults, and in over 40 countries for add-on treatment of pediatric patients with partial epilepsy (with or without other idiopathic generalized seizure types). In addition, LTG is licensed in some countries as initial monotherapy for partial seizures in patients over the age of 12 years, and in some countries as conversion to monotherapy for partial seizures in children aged 2-12 years. In the US, LTG is approved as adjunctive therapy in adult and pediatric patients (≥ 2 years of age) with partial seizures or with the generalized seizures of Lennox-Gastaut syndrome. LTG is also approved for conversion to monotherapy in adults with partial seizures who are receiving treatment with a single enzyme-inducing anti-epileptic drug (e.g., carbamazepine) or valproate.

The information provided in the current application supports the efficacy and safety of LTG as adjunctive therapy for treatment of primary generalized tonic-clonic (PGTC) seizures in pediatric and adult patients. The application consists of a single pivotal study to support this indication. Study LAM40097 was the subject of an October 6, 2000 teleconference between representatives of the Agency and GlaxoSmithKline. The Agency agreed that LAM40097, along with supportive data from other studies evaluating LTG in related seizure types, could serve as the basis for approval of LTG as adjunctive treatment of PGTC seizures in pediatric and adult patients, provided the results were sufficiently robust.

The primary objective of this study was to assess the efficacy of LTG adjunctive therapy in subjects with PGTC seizures. This was a double-blind, randomized, placebo-controlled, parallel-group, multicenter study. The study comprised a Screen and three phases: Baseline (8 weeks), Dose Escalation (12 weeks for subjects 2-12 years of age and 7 weeks for subjects >12 years of age), and Maintenance (12 weeks). Subjects attended the clinic for safety and efficacy evaluations at Baseline Weeks 4 and 8, and at Treatment Weeks 3, 7, 11, 15, and 19 (subjects >12 years of age) or Treatment Weeks 3, 7, 11, 15, 19, and 24 (subjects 2-12 years of age). A total of 117 subjects were randomized and received double-blind study drug (58 received LTG and 59 received matched placebo). There were total of 52 centers in this study: 45 in the USA, 4 in Argentina, 2 in Chile and 1 in Peru.

2.2 Data Sources

The path to the CDER Electronic Document Room (EDR) is:

\\Cdsesub1\n20241\S_027\2005-02-04 and \\Cdsesub1\n20764\S_020\2005-02-04

3. Statistical Evaluation

3.1 Evaluation of Efficacy

Text, tables and figures presented in Section 3.1.1 to 3.1.7 are mainly from the applicant's submission.

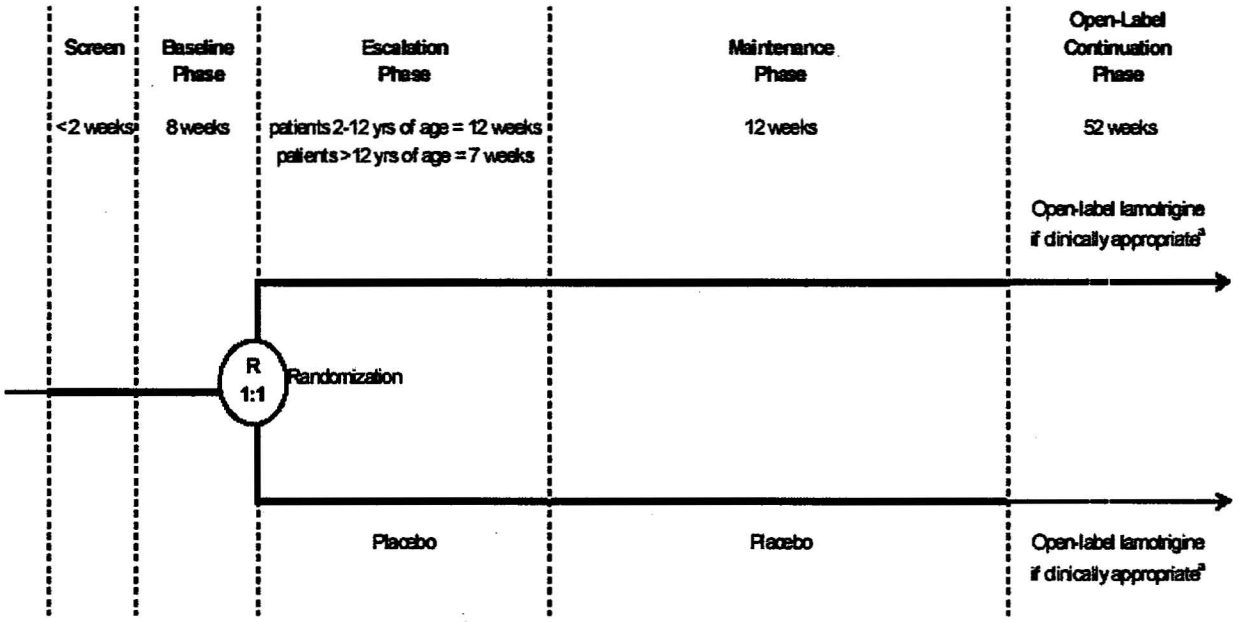
3.1.1 Objective of Study

The primary objective of this study was to assess the efficacy of LTG adjunctive therapy in subjects with PGTC seizures.

3.1.2 Study Design

This study was an international, multicenter, double-blind, randomized, placebo controlled, parallel-group study to evaluate the efficacy, safety, and health outcomes of LTG as adjunctive therapy, compared to placebo, for the treatment of PGTC seizures. The study design is summarized in Figure 3.1.2.1.

Figure 3.1.2.1 Study Design



The trial consisted of a Screen and three Phases (i.e., Baseline, dose Escalation, Maintenance) that lasted 32 weeks for subjects who were 2-12 years of age, and lasted 27 weeks for subjects who were >12 years of age. The reason for these differing lengths was that the Escalation Phase for subjects aged 2-12 years was longer than that for subjects >12 years of age. The three phases of the trial were: 8 weeks Baseline Phase; 12 weeks for subjects 2-12 years of age, and 7 weeks for subjects >12 years of age Escalation Phase; and 12 weeks Maintenance Phase.

The main criteria for inclusion was a confident diagnosis of epilepsy with PGTC seizures (with or without other idiopathic generalized seizure types) currently treated with a stable regimen of one or two anti-epileptic drugs (AEDs) for at least 4 weeks prior to starting the Baseline Phase were eligible for this study. Seizures had to be easily recognizable by the subject and/or parent/caregiver and classifiable by the International Classification of Seizures.

Seizure count was assessed at every clinic visit by review of daily diary. Adverse events (AEs), concurrent medications and AEDs were reviewed. Weight and height were recorded at all scheduled visits. Four patient reported outcome questionnaires [the Beck Depression Inventory (BDI-II), the Cornell Dysthymia Rating Scale: Self-Report (CDRS-SR), the Profile of Mood States (POMS), and the Quality of Life in Epilepsy Questionnaire (QOLIE-31)] were administered at Screen and at the end of the treatment period.

All randomized subjects who completed the Maintenance Phase or withdrew prematurely from the study treatment due to exacerbation of their seizure activity or to intolerable, but not medically serious, side effects were offered the option to participate in an open-label Continuation Phase for a long-term follow up and receive open-label LTG, if clinically appropriate, for up to 1 year (52 weeks). Subjects who failed to meet the minimum number of PGTC seizures during the prospective Baseline Phase were allowed to enroll in the open-label Continuation Phase, if clinically appropriate, for up to 5 months. For this clinical study report, the cut-off date for the Continuation Phase was 30 September 2004. Data received in-house on or before this date regarding deaths, SAEs, and pregnancies are provided for the Continuation Phase. Complete results from the open-label Continuation Phase will be presented in a separate report.

Dosing Schedule: If randomized to LTG, subjects were assigned to one of 3 dosing schedules depending on their concurrent AED(s): 1. A dosing schedule for subjects taking concurrent valproic acid (VPA) with or without another AED; 2. A dosing schedule for subjects taking a concurrent EIAED (enzyme-inducing antiepileptic drug), with or without another AED other than VPA; and 3. A dosing schedule for subjects taking concurrent AED(s) other than VPA and EIAEDs (For purposes of this study, the major EIAEDs were defined as carbamazepine, phenytoin, phenobarbital and primidone.)

The dosing schedules, describing starting doses, target doses, minimum and maximum allowable doses, and dose adjustments are presented in Table 3.1.2.1 and Table 3.1.2.2.

Table 3.1.2.1 Lamotrigine Dosing in Subjects 2-12 Years of Age

	ESCALATION										MAINTENANCE
Concurrent Therapy	**Treatment Weeks 1-2**	**Treatment Weeks 3-4**	**Treatment Week 5**	**Treatment Week 6**	**Treatment Week 7**	**Treatment Week 8**	**Treatment Week 9**	**Treatment Week 10**	**Treatment Week 11**	**Treatment Week 12**	**Treatment Weeks 13-24**
Subjects taking VPA (with or without another AED)	0.15 mg/kg/day (1 dose or 2 divided doses)	0.3 mg/kg/day (1 dose or 2 divided doses)	0.6 mg/kg/day (2 divided doses)	0.9 mg/kg/day (2 divided doses)	1.2 mg/kg/day (2 divided doses)	1.5 mg/kg/day (2 divided doses)	1.8 mg/kg/day (2 divided doses)	2.1 mg/kg/day (2 divided doses)	2.4 mg/kg/day (2 divided doses)	2.7 mg/kg/day (2 divided doses)	**Target dose: 3mg/kg/day[a] (up to maximum of 200mg/day) (2 divided doses)**
Subjects taking an EIAED[d] (with or without another AED other than VPA)	0.6 mg/kg/day (2 divided doses)	1.2 mg/kg/day (2 divided doses)	2.4 mg/kg/day (2 divided doses)	3.6 mg/kg/day (2 divided doses)	4.8 mg/kg/day (2 divided doses)	6 mg/kg/day (2 divided doses)	7.2 mg/kg/day (2 divided doses)	8.4 mg/kg/day (2 divided doses)	9.6 mg/kg/day (2 divided doses)	10.8 mg/kg/day (2 divided doses)	**Target dose: 12mg/kg/day[b] (up to a maximum of 400mg/day) (2 divided doses)**
Subjects taking AED(s) other than VPA and EIAEDs[d]	0.3 mg/kg/day (1 dose or 2 divided doses)	0.6 mg/kg/day (2 divided doses)	1.2 mg/kg/day (2 divided doses)	1.8 mg/kg/day (2 divided doses)	2.4 mg/kg/day (2 divided doses)	3.0 mg/kg/day (2 divided doses)	3.6 mg/kg/day (2 divided doses)	4.2 mg/kg/day (2 divided doses)	4.8 mg/kg/day (2 divided doses)	5.4 mg/kg/day (2 divided doses)	**Target dose: 6mg/kg/day[c] (up to a maximum of 300mg/day) (2 divided doses)**

a. If a subject could not tolerate 3mg/kg/day, the dose was decreased to a minimum of 2.25mg/kg/day. If seizure control was inadequate, the dose was increased to 3.75mg/kg/day up to a maximum of 200mg/day.
b. If a subject could not t tolerate 12mg/kg/day, the dose was decreased to a minimum of 9.0mg/kg/day. If seizure control was inadequate, the dose was increased to 15.0mg/kg/day up to a maximum of 400mg/day.
c. If a subject could not tolerate 6mg/kg/day, the dose was decreased to a minimum of 4.5mg/kg/day. If seizure control was inadequate, the dose was increased to 7.5mg/kg/day up to a maximum of 300mg/day.
d. For purposes of this study, the major EIAEDs included carbamazepine, phenytoin, phenobarbital and primidone.

Note: If necessary, doses were rounded down to the nearest 2mg. Subjects who did not convert to open-label lamotrigine had their study drug tapered off over at least 2 weeks, by approximately 50% per week, unless safety concerns required a more rapid withdrawal.

Table 3.1.2.2 Lamotrigine Dosing in Subjects >12 Years of Age

	ESCALATION					MAINTENANCE
Concurrent Therapy	**Treatment Weeks 1-2**	**Treatment Weeks 3-4**	**Treatment Week 5**	**Treatment Week 6**	**Treatment Week 7**	**Treatment Weeks 8-19**
Subjects taking VPA (with or without another AED)	12.5mg/day (given as 25mg every *other* day)	25mg/day (once daily)	50mg/day (2 divided doses)	100mg/day (2 divided doses)	150mg/day (2 divided doses)	Target dose: 200mg/day[a] (2 divided doses)
Subjects taking an EIAED[d] (with or without another AED other than VPA)	50mg/day (2 divided doses)	100mg/day (2 divided doses)	150mg/day (2 divided doses)	200mg/day (2 divided doses)	300mg/day (2 divided doses)	Target dose: 400mg/day[b] (2 divided doses)
Subjects taking AED(s) other than VPA and EIAEDs[d]	25mg/day (once daily)	50mg/day (2 divided doses)	100mg/day (2 divided doses)	150mg/day (2 divided doses)	200mg/day (2 divided doses)	Target dose: 300mg/day[c] (2 divided doses)

a If a subject could not tolerate 200mg/day, the dose was decreased to a minimum of 150mg/day. If seizure control was inadequate, the dose was increased to a maximum of 250mg/day.
b If a subject could not tolerate 400mg/day, the dose was decreased to a minimum of 300mg/day. If seizure control was inadequate, the dose was increased to a maximum of 500mg/day.
c If a subject could not tolerate 300mg/day, the dose was decreased to a minimum of 225mg/day. If seizure control was inadequate, the dose was increased to a maximum of 375mg/day.
d For purposes of this study, the major EIAEDs included carbamazepine, phenytoin, phenobarbital and primidone.

Note: Subjects who did not convert to open-label lamotrigine had their study drug tapered off over at least 2 weeks, by approximately 50% per week, unless safety concerns required a more rapid withdrawal.

3.1.3 Efficacy Measures

The primary efficacy endpoint was percent change from Baseline in average monthly PGTC seizure frequency.

Subjects recorded the number of seizures, by seizure type, as well as duration of episodes of innumerable seizure activity in their daily diaries during all phases of this study. If the subjects experienced myoclonic seizures, the number of days on which myoclonus occurred was recorded. The site personnel transcribed the diary information into the CRF, with the diary pages serving as source documentation.

Secondary efficacy endpoints included the proportions of subjects with ≥ 25%, ≥ 50%, ≥ 75%, or 100% reduction in PGTC seizures; the proportions of subjects with ≥ 25%, ≥ 50%, ≥ 75%, or 100% reduction in all seizures; the percentage change from Baseline in average monthly seizure frequency (all seizure types); and the percentage change from Baseline in average cumulative biweekly PGTC seizure frequency.

3.1.4 Statistical Analysis Plan

All efficacy analyses were performed using the ITT population. In addition, the primary analysis and key secondary analyses were performed using the Efficacy population and Completers population. Average monthly seizure frequency, defined as the number of seizures divided by the number of days in the Baseline or analyzed treatment time period multiplied by 28 days, were computed for each subject in order to derive the percent change from Baseline in seizure frequency. For subjects who withdraw from the study, seizure data were averaged for the portion of the study the subject completed up to the time of study drug discontinuation. If a subject withdrew before the Maintenance Phase, the seizure data from the Escalation Phase were carried forward for the Maintenance Phase. If a subject withdrew during the Maintenance Phase, only seizure data from the Maintenance Phase were included in the average monthly seizure frequency for the Maintenance Phase.

The primary analysis was a two-way analysis of variance (ANOVA) based on ranks with treatment group and age category as predictor variables. Seizure frequencies during the entire treatment period and the Maintenance Phase was considered separately for analysis.

Sample size: Approximately 150 subjects from approximately 70 sites were planned to be enrolled. Assuming a 30% Baseline drop rate, it was projected that approximately 150 subjects would be enrolled in order to randomize 104 subjects. Assuming a 20% Treatment drop rate, it was projected that approximately 80 subjects would complete the Maintenance Phase. One hundred four (104) subjects would provide at least 80% power for detection of a significant difference of 25% in the median percent reduction from baseline in PGTC seizures using an estimate of the standard deviation of 45% at a significance level of 0.05. Eighty (80) subjects would provide at least 80% power for detection of a significant difference of 30% in the median percent reduction from baseline in PGTC

seizures using an estimate of the standard deviation of 45% at a significance level of 0.05. Subjects were stratified by age as follows: Subjects 2-12 Years of Age and > 12 Years of Age.

3.1.5 Protocol Amendments

The protocol was amended three times. All of the amendments applied to every site.

Amendment 1 (dated April 20, 2001) revised the enrollment criteria to change the required number of PGTC seizures prior to and during the Baseline Phase (from "at least 3 PGTC seizures during the 8-week Baseline phase, with at least 1 PGTC seizure occurring in each 4-week period of the Baseline", to "at least 3 PGTC seizures occurring anytime during the entire 8-week Baseline Phase") and allowed the use of a historical baseline or a combination of historical and prospective baseline. It also allowed investigators to use a historical EEG (electroencephalogram) (if available) to enroll a subject, and provided guidelines for the use of historical EEGs. Subjects with vagal nerve stimulation (VNS) were also allowed to enroll, and revised guidelines for the acute and chronic daily use of benzodiazepines were provided. Body weight was added as a secondary endpoint. A total of 27 subjects were enrolled at the time of this amendment.

Amendment 2 (dated March 8, 2002) clarified definitions of analysis populations and power calculations, with subsequent changes to the number of participating sites and the number of subjects. A total of 63 subjects were enrolled at the time of this amendment.

Amendment 3 (dated February 10, 2003) revised the protocol to permit participation of non-US sites (non-US sites were also enrolled under the US IND). A total of 122 subjects were enrolled at the time of this amendment.

3.1.6 Study Population

A total of 117 subjects were randomized and received at least one dose of study drug. Fifty-eight subjects were randomized to the LTG group and 59 subjects were randomized to the placebo group. A greater percentage of subjects in the placebo group (7%) compared with the LTG group (0 subjects) were prematurely discontinued due lack of efficacy; a greater percentage of subjects in the LTG group (9%) compared with the placebo group (3%) were prematurely discontinued due an AE; likewise, a greater percentage of subjects in the LTG group (9%) compared with the placebo group (2%) was prematurely discontinued due to "lost to follow-up." Subject 8957 (placebo group) was prematurely discontinued due to an increased number of PGTC seizures (reason for premature withdrawal was "Other").

Subject accountability is summarized in Table 3.1.6.1.

Table 3.1.6.1 Subject Accountability (ITT)

	Number (%) of Subjects	
	LTG N=58	PBO N=59
Completion Status		
Completed Study	42 (72)	45 (76)
Prematurely Withdrawn	16 (28)	14 (24)
Reason for Premature Withdrawal		
Adverse Event	5 (9)	2 (3)
Consent Withdrawn	2 (3)	0
Lack of Efficacy	0	4 (7)
Lost to Follow-Up	5 (9)	1 (2)
Non-compliance	4 (7)	6 (10)
Other	0	1 (2)

Note: Other= increased number of PGTC seizures

The Intent-to-Treat (ITT) population consisted of all subjects who were randomized and took at least one dose of study drug. The Efficacy population consisted of all subjects in the ITT population excluding subjects with major protocol violations. The Completers population consisted of all subjects who completed the entire blinded treatment period. A summary of patients comprising each of the populations represented in this report is shown in Table 3.1.6.2.

Table 3.1.6.2 Summary of Populations Analyzed

Subject Population	LTG	PBO
Intent-to-Treat	58	59
Efficacy	53	52
Completers	42	45

Demographic characteristics for the ITT population are summarized in Table 3.1.6.3.

Table 3.1.6.3 Demographic Characteristics (ITT)

Demographic Characteristic	LTG N=58	PBO N=59
Gender, n (%)		
Male	29 (50)	33 (56)
Female	29 (50)	26 (44)
Age (yr)		
Mean (SD)	26.9 (14.6)	24.9 (13.8)
Range	2-53	2-55
Race, n (%)		
White	33 (57)	28 (47)
Black	9 (16)	10 (17)
Hispanic	16 (28)	21 (36)
Age Stratum, n (%)		
2-12 years	12 (21)	11 (19)
>12 years	46 (79)	48 (81)

A summary of seizure history and epilepsy classification at Screening is provided in Table 3.1.6.4.

Table 3.1.6.4 Seizure History and Epilepsy Classification at Screening (ITT)

Characteristic	LTG N=58	PBO N=59
Seizure Etiology, n (%)		
Idiopathic	48 (83)	45 (76)
Symptomatic	4 (7)	8 (14)
Cryptogenic	6 (10)	6 (10)
Mean Age at First Seizure (yrs) (SD)	11.9 (10.5)	12.1 (8.6)
All Seizure Classifications, n (%)		
Any Seizure Type	58 (100)	59 (100)
D1 (absence)	18 (31)	20 (34)
D2 (myoclonic)	17 (29)	16 (27)
D3 (clonic)	1 (2)	3 (5)
D4 (tonic)	5 (9)	6 (10)
D5 (generalized tonic-clonic)	58 (100)	59 (100)
D6 (atonic)	1 (2)	1 (2)
E (unclassified)	1 (2)	0
Number of Seizures per Month, Mean (SD)		
D5 Seizures Mean (SD)	4.08 (5.77)	5.83 (13.97)
D5 Seizures Median	2.43	2.85
All Seizures Mean (SD)	48.56 (296.07)	19.63 (50.83)
All Seizures Median	3.63	3.88
No. of concurrent AEDs		
1	29 (50)	35 (59)
2	29 (50)	24 (41)

Data on the type of baseline are summarized in Table 3.1.6.5.

Table 3.1.6.5 Type of Baseline Data (ITT)

Type of Baseline	LTG N=58 n (%)	PBO N=59 n (%)
Combination	25 (43)	28 (47)
Historical	10 (17)	12 (20)
Prospective	23 (40)	19 (32)

The type of baseline (prospective, historical, or combination) was similar between the two treatment groups. A total of 95% of subjects in each treatment group had at least three PGTC seizures during the Baseline Phase.

A summary of concurrent AED therapy is provided in Table 3.1.6.6.

Table 3.1.6.6 Concurrent AED Therapy (ITT)

Concurrent AED Therapy	LTG N=58 n (%)	PBO N=59 n (%)
VPA (with or without another AED)	25 (43)	28 (47)
EIAED (without VPA)	27 (47)	24 (41)
Other (no VPA and no EIAED)	6 (10)	7 (12)

Concurrent AED therapy was similar between the two treatment groups.

3.1.7 Applicant's Efficacy Results

The median percent change from Baseline in PGTC seizure frequency was the primary efficacy endpoint. The median percent change from Baseline in seizure frequency for PGTC seizures for the Escalation Phase, the Maintenance Phase, and the entire treatment period for the ITT Population are summarized in Table 3.1.7.1. P-value was from a two-way analysis of variance (ANOVA) based on ranks with treatment group and age category as predictor variables.

Table 3.1.7.1 Median Percent Change in PGTC Seizure Frequency (ITT)

Study Period	LTG N=58	PBO N=59	p value
	Median (range)	Median (range)	
Escalation	-60.63 (-100.0, 83.7)	-32.83 (-100.0, 430.6)	0.038
Maintenance	-81.90 (-100.0, 239.1)	-42.97 (-100.0, 782.2)	0.006
Entire Trt	-66.47 (-100.0, 144.9)	-34.20 (-100.0, 430.6)	0.006

Trt=Treatment Period

The median percent change from Baseline in PGTC seizure frequency was statistically significantly greater in the LTG group than in the placebo group for the Escalation Phase, the Maintenance Phase, and the entire treatment period.

The median percent change from Baseline in PGTC seizure frequency for the Escalation Phase, the Maintenance Phase, and the entire treatment period for the Completers Population is provided in Table 3.1.7.2.

Table 3.1.7.2 Median Percent Change in PGTC Seizure Frequency (Completers)

Study Period	LTG N=42	PBO N=45	p-value
	Median (range)	Median (range)	
Escalation	-46.48 (-100.0, 83.7)	-32.83 (-100.0, 168.9)	0.531
Maintenance	-69.96 (-100.0, 239.1)	-42.97 (-100.0, 782.2)	.030
Entire Trt	-53.21 (-100.0, 144.9)	-34.20 (-100.0, 379.8)	0.139

3.1.8 Reviewer's Analysis

The reviewer validated the applicant's results according to the protocol.

Theoretically the ANOVA based on ranks test whether two distributions are identical, which may or may not imply that their medians are different. This reviewer applied nonparametric median test which gives p-value .0043.

Analysis by Withdrawals

Table 3.1.8.1 presents the median percent change from baseline at the end for both completers and withdrawals. LTG is numerically better than placebo for both groups.

Table 3.1.8.1 Median Percent Change in PGTC Seizure Frequency Completers and Withdrawals

Study Period Entire Trt	LTG		PBO	
	N	Median (range)	N	Median (range)
Completers	42	-53.21 (-100.0, 144.9)	45	-34.20 (-100.0, 379.8)
Withdrawals	16	-94.30 (-100.0, -10.45)	14	-26.96 (-100.0, 430.6)

Table 3.1.8.2 presents the mean average dose for withdrawals.

Table 3.1.8.2 Mean Average Dose for Withdrawals and Others

Study Period	LTG Withdrawals		LTG Others		LTG All	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Escalation	16	62.7 (49.1)	42	99.6 (39.7)	58	89.4 (45.2)
Maintenance	8	178.4 (132.1)	42	293.0 (109.3)	50	274.7 (119.5)

The above table doesn't indicate that withdrawals in LTG group were in average higher dose than others in LTG group.

Analysis by Age

The applicant presented percent change from Baseline in Seizure frequency for patients in 2-16 years old. The following table lists median change in 2-16 years old. P-value is calculated from ANOVA based on ranks with terms for treatment group.

Table 3.1.8.2 Median Percent Change in PGTC Seizure Frequency (2-16 years old)

Study Period	LTG N=16	PBO N=20	p-value
	Median (range)	Median (range)	
Entire Trt	-72.94 (-100.0, 31.9)	-42.23 (-100.0, 379.8)	0.2558

The following table lists median change in 2-12 years old. P-value is calculated from ANOVA based on ranks with terms for treatment group.

Table 3.1.8.3 Median Percent Change in PGTC Seizure Frequency (2-12 years old)

Study Period	LTG N=12	PBO N=11	p-value
	Median (range)	Median (range)	
Entire Trt	-79.72 (-100.0, 31.9)	-43.47 (-100.0, 379.8)	0.8578

In both 2-16 and 2-12 groups, LTG group is numerically better than placebo group but none is statistically significant because sample sizes are not planned for the analytical comparisons.

The following table lists median change in 2-5 years old and 6-12 years old groups.

Table 3.1.8.4 Median Percent Change in PGTC Seizure Frequency (2-5 and 6-12 years old)

Study Period Entire Trt	LTG		PBO	
	N	Median (range)	N	Median (range)
2-5	4	9.46 (-96.4, 31.9)	5	-71.2 (-100.0, -6.3)
6-12	8	-84.39 (-100.0, -13.7)	6	-30.65 (-100.0, 379.8)

The following table lists age distribution in 2-5 years old and 6-12 years old groups.

Table 3.1.8.5 Age Distributions for 2-5 and 6-12 Years Old

Study Period Entire Trt	LTG	PBO
	Age	Age
2-5	2, 4, 4, 5	2, 3, 4, 5, 5
6-12	6, 6, 7, 8, 9, 10, 11, 12	6, 6, 7, 8, 9, 11

Analysis by Country

The Study was conducted in four countries. The following table presents the median percent change from baseline at the end by the country.

Table 3.1.8.4 Median Percent Change in PGTC Seizure Frequency by Country

Entire Trt Period	LTG		PBO		Difference
	N	Median (range)	N	Median (range)	
USA	45	-63.98 (-100.0, 46.6)	44	-21.5 (-100.0, 430.6)	-42.48
Argentina	10	-79.7 (-100.0, 144.9)	10	-54.5 (-100.0, 122.8)	-25.2
Peru	3	-10.45 (-100.0, 31.0)	3	-90.46 (-100.0, -58.6)	80.01
Chile			2	-36.7 (-39.3, -34.2)	

In Peru, placebo group is numerically better than LTG group.

Analysis by Center

There were 38 centers with patients included in the ITT. Table 3.1.8.4 presents number of subjects, median percent change from Baseline at the end in PGTC Seizure frequency, and difference between LTG and placebo.

Table 3.1.8.5 Median Percent Change from Baseline by Center

Obs	Center	LTG	media_LTG	PBO	media_PBO	difference
1	010059	2	-20.789	1	225.429	-246.217
2	010586	8	-53.212	5	-47.588	-5.624
3	011714	1	-85.689	.	.	.
4	012241	3	-21.138	2	-81.223	60.085
5	012325	.	.	1	97.992	.
6	012490	2	-98.215	.	.	.
7	013720	.	.	3	-25.550	.
8	013755	.	.	1	114.717	.
9	014615	1	-64.101	.	.	.
10	014834	1	-100.000	.	.	.
11	015144	3	-36.137	3	-17.912	-18.224
12	015908	.	.	2	-38.636	.
13	016536	1	-71.583	.	.	.
14	016707	2	-80.357	.	.	.
15	016776	1	-29.429	2	5.139	-34.568
16	016800	.	.	1	-6.349	.
17	017002	.	.	1	-15.901	.
18	017053	1	-100.000	2	128.617	-228.617
19	017314	1	-54.167	2	189.463	-243.630
20	017411	3	-37.210	4	-24.019	-13.190
21	017586	1	-33.276	.	.	.
22	018388	1	-100.000	.	.	.
23	019064	.	.	1	-40.690	.
24	019652	2	-80.364	1	-68.338	-12.026
25	019828	2	-93.257	4	-49.630	-43.627
26	019843	1	-21.326	1	-100.000	78.674
27	020260	3	-100.000	2	26.903	-126.903
28	020623	1	-100.000	.	.	.
29	020924	2	22.430	.	.	.
30	020994	4	-83.790	7	-100.000	16.210
31	021036	4	-21.438	3	-20.307	-1.131
32	021484	.	.	2	-36.729	.
33	021517	2	-66.037	2	-2.108	-63.929
34	021794	3	-10.454	3	-90.459	80.005
35	022148	2	-0.735	.	.	.
36	022316	.	.	1	61.225	.
37	025416	.	.	1	-19.231	.
38	030104	.	.	1	-62.289	.

There are 12 centers (75%) where LTG group is numerically better than placebo group among centers enrolled both LTG and placebo patients. Since large changes are usually seen in centers with few patients, outlier issue is hard to address for this sparse data.

3.2 Evaluation of Safety

See Clinical Review.

4. Findings in Special/Subgroup Populations

4.1 Gender, Race, and Age

Table 4.1.1 gives median percent change from baseline at the end in seizure frequency for the entire treatment period by gender and race. LTG group is numerically better than placebo group in all subgroups.

Table 4.1.1 Median Percent Change in PGTC Seizure Frequency (ITT)

		LTG		PBO	
		N	median (range)	N	median (range)
Gender	Male	29	-72.13 (-100.0, 46.6)	33	-39.26 (-100.0, 430.6)
	Female	29	-62.79 (-100.0, 144.9)	26	-22.04 (-100.0, 379.8)
Race	White	33	-69.29 (-100.0, 35.0)	28	-21.73 (-100.0, 188.6)
	Black	9	-62.79 (-100.0, -13.7)	10	18.98 (-90.5, 430.6)
	Hispanic	16	-74.41 (-100.0, 144.9)	21	-58.61 (-100.0, 122.8)

Table 4.1.2 gives median percent change from baseline at the end in seizure frequency for the entire treatment period by age groups.

Table 4.1.2 Median Percent Change in PGTC Seizure Frequency (ITT)

	LTG		PBO	
	N	median (range)	N	median (range)
2-16	16	-72.94 (-10.0, 31.9)	20	-42.23 (-100.0, 379.8)
2-12	12	-79.72 (-100.0, 31.9)	11	-43.47 (-100.0, 379.8)
2-5	4	9.46 (-96.4, 31.9)	5	-71.2 (-100.0, -6.3)
6-12	8	-84.39 (-100.0, -13.7)	6	-30.65 (-100.0, 379.8)

4.2 Other Special/Subgroup Populations

There is no analysis performed for other populations.

5. Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The data and analyses from Study LAM40097 showed that there was a statistically significant difference in favor of LTG, compared to placebo, for the median percent change in PGTC seizure frequency from baseline at the end in the ITT population.

The median percent change in PGTC seizure frequency from baseline at the end in the ITT population was -66.47 with range -100.0 to 144.9 for 58 patients in LTG group, and -34.20 with range -100.0 to 430.6 for 59 patients in placebo group, respectively. The ANOVA based on ranks with treatment group and age category as predictor variables for analyzing the median percent change had p-value .006.

For patients between 2-16 years old, the median percent change in PGTC seizure frequency from baseline at the end in the ITT population was -72.94 with range -100.0 to 31.9 for 16 patients in LTG group, and -42.23 with range -100.0 to 379.8 for 20 patients in placebo group, respectively.

For patients between 2-12 years old, the median percent change in PGTC seizure frequency from baseline at the end in the ITT population was -79.72 with range -100.0 to 31.9 for 12 patients in LTG group, and -43.47 with range -100.0 to 379.8 for 11 patients in placebo group, respectively.

Since the sample size calculation is not based on the analytical comparisons for the lower age groups of 2-12 and 2-16, statistical tests based on ANOVA are not significant for the lower age groups. Although LTG is numerically better than placebo in the lower age groups, it is hard to judge whether the evidence is convincing due to few subjects in the lower age groups.

5.2 Conclusions and Recommendations

The data from Study LAM40097 provided evidence that there was a statistically significant difference in favor of LTG as adjunctive therapy for treatment of PGTC seizures in pediatric and adult patients, compared to placebo, for the median percent change in PGTC seizure frequency from baseline at the end in the ITT population.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-241/S-027 and 20-764/S-020

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA:	20-241/SLR-021, 025, 026, 027, (b) 20-764/SLR-014, 018, 019, 020, (b) (4)
Brand Name:	Lamictal®
Generic Name:	Lamotrigine
Sponsor:	GlaxoSmithKline
Type of Dosage Form:	Tablets and Chewable Dispersible Tablets
Strengths:	25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg
Indications:	Treatment of Primary Generalized Tonic-Clonic Seizures
OCP Reviewer:	Ta-Chen Wu, Ph.D.
OCP Team Leader:	Ramana S. Uppoor, Ph.D.
OCP Division:	DCP-1 HFD-860
OND Division:	Neurology Drug Products HFD-120
Submission Date:	March 22, 2006
Type of Submission:	Response to the AE Letter

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1. EXECUTIVE SUMMARY

1.1. BACKGROUND

Lamotrigine (Lamictal®) Tablets and Chewable Dispersible Tablets of 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg strengths were developed by the GlaxoSmithKline as adjunctive use for the treatment of primary generalized tonic-clonic (PGTC) seizures for adults and pediatric patients above 2 years old, along with partial seizures and the generalized seizures of Lennox-Gastaut syndrome in approved label.

The current submission contains sponsor's complete responses to the approvable (AE) letter dated December 7, 2005 for NDA 20-241 and NDA 20-764 applications, with the exception of comments relative to (b) (4) . These applications, including both prior approval supplements and "Changes Being Effected" (CBE) supplements, are summarized in the table below:

Supplement Number	Submission Date	Provisions of Supplement
NDA 20-241/S-027 NDA 20-764/S-020	February 4, 2005	Prior approval supplement: adjunctive treatment of primary generalized tonic-clonic (PGTC) seizures
(b) (4)		
NDA 20-241/S-021 NDA 20-764/S-014	May 29, 2003	CBE: Revised wording under PRECAUTIONS; Dermatologic Effects, DOSAGE AND ADMINISTRATION, Patient Information, and CLINICAL PHARMACOLOGY: Mechanism of Action
NDA 20-241/S-025 NDA 20-764/S-018	June 29, 2004	CBE: Revised wording under CLINICAL PHARMACOLOGY; Drug Interactions, and DOSAGE AND ADMINISTRATION
NDA 20-241/S-026 NDA 20-764/S-019	August 20, 2004	CBE: Revised Patient Information Leaflet

At the telecon on December 19, 2005, the Agency encouraged a full response to the AE letter but agreed to consider a partial response in the event that the sponsor needs to (b) (4) However, the sponsor was requested to fully address the safety-related comments.

Issues in the AE Letter conveyed to the Sponsor include the (b) (4) , oral contraceptives (OC), replacement of "enzyme-inducing AEDs" with the specific drug names, (b) (4) , drug-drug interactions, labeling, promotional materials, and the original OCP comment made by Dr. Andre Jackson on drug-drug interactions, as shown below:

Original OCP review comments:
The firm has not supplied any supportive data for tiagabine and for gabapentin as interacting drugs with Lamictal. For tiagabine there may be reason for concern since it is recommended that it be (b) (4) *with Lamictal. On the other hand, gabapentin is renally excreted so it is unlikely to interact however, there is no experimental data on its interaction with Lamictal.*

Lamotrigine is primarily metabolized by uridine 5'-diphosphate glucuronosyltransferase (UGT1A4) via N-glucuronidation to form 2-N-glucuronide conjugate, an inactive metabolite excreted in the urine. The previously noted drug-drug interaction that has clinical relevance involves the inhibition of UDPGT activity by valproate, resulting in a need for dose adjustment (i.e., 50% reduction) for lamotrigine. According to the approved label for Lamictal®, oral contraceptives containing 30 µg ethinylestradial and 150 µg levonorgestrel increased the clearance of lamotrigine (by approximately 2 fold). Effect of other hormonal contraceptive preparations or hormone replacement therapy on the PK of lamotrigine have not been evaluated, but similar dosage adjustment for Lamictal® may be needed, based on clinical responses.

The Sponsor has provided justifications based on provided journal articles for not conducting PK drug interaction studies as conveyed by the Agency in AE Letter. This review will focus primarily on the Sponsor's response to the OCP comment (Agency's Comment 5) concerning potential drug-drug interactions, Special Population section of the labeling regarding clearance-based dose adjustment in patients with hepatic impairment, and updated labeling language regarding race. The tolerability issues will be reviewed in greater details by the Medical Officer, but as requested, additional OCP comments will be made on the Sponsor's responses to Agency's Comment 2 concerning the tolerability issue for higher lamotrigine doses in women who are taking concomitant hormonal oral contraceptives.

1.2. SPONSOR'S RESPONSES TO THE AGENCY'S COMMENTS

Agency Comment 5:
We ask that you formally study the interaction of lamotrigine with tiagabine. You should also further address the potential for interaction between lamotrigine and gabapentin and between lamotrigine and pregabalin.

Sponsor Response:
Tiagabine:
Based on the following information, GSK believe that the rationale for performing a formal drug-drug interaction study based on pharmacokinetic grounds alone is limited, as a clinically significant pharmacokinetic interaction between lamotrigine and tiagabine is unlikely.

Lamotrigine is hepatically metabolized primarily by glucuronic acid conjugation (UGT1A4). The major metabolite is an inactive 2-N-glucuronide conjugate. Following oral administration of 240 mg of ^{14}C-lamotrigine to healthy volunteers (N=6), 94% of drug related material was recovered in urine and 2% was recovered in feces. The urinary contents consisted of unchanged lamotrigine (10%), the 2-N-glucuronide (76%), a 5-N-glucuronide (10%), a 2-N-methyl metabolite (0.14%) and another unidentified minor metabolite (4%). Consistent with this, lamotrigine clearance is decreased when it is co-administered with the glucuronidation inhibitor, valproate. Hepatic enzyme-inducing agents increase the clearance of lamotrigine. Drugs such as carbamazepine, phenytoin, phenobarbital or primidone, rifampin, and oral contraceptives are believed to achieve this by induction of glucuronidation capacity.

Lamotrigine has been shown to have no appreciable effect on the clearance of phenytoin (primarily metabolized by oxidation, CYP2C, some glucuronidation), nor on carbamazepine (oxidation, CYP3A & CYP2C and glucuronidation), oxcarbazepine or levetiracetam. A small, but clinically insignificant decrease in valproate exposure was observed (-25%) in healthy volunteers. In patients, no change in valproate plasma concentrations in either adults or pediatric patients was observed in controlled clinical trials when coadministered with LAMICTAL.

Tiagabine is primarily cleared by hepatic metabolism via oxidation of the thiophene rings and to a small extent glucuronidation. In contrast to lamotrigine the clearance of tiagabine was unaffected when coadministered with valproate supporting evidence that glucuronidation is a minor route in the clearance of tiagabine. In-vivo, the clearance of tiagabine has been shown to be significantly increased when coadministered with hepatic enzyme-inducing drugs such as carbamazepine, phenytoin, phenobarbital or primidone which is believed to be achieved by the induction of CYP3A capacity [Brodie et al., 1995, Samara et al., 1998]. Similar to lamotrigine, little or no effect of tiagabine has been observed on the clinical pharmacokinetics of enzyme-inducing AEDs (phenytoin, carbamazepine, phenobarbital or primidone) or valproate (-10% decrease in steady-state valproate concentrations was observed).

In terms of safety and tolerability with coadministration of tiagabine and LAMICTAL, we believe it is unlikely that the safety/tolerability profile is altered during coadministration in comparison to the profile associated with each drug respectively.

In conclusion, given the apparent minor role of glucuronidation in the clearance of tiagabine as indicated by the lack of pharmacokinetic interaction with valproate and the lack of effect of enzyme inhibition/induction potential of lamotrigine, there is a low likelihood of tiagabine inducing or inhibiting the metabolism of lamotrigine under steady-state lamotrigine conditions or of lamotrigine inhibiting or inducing the metabolism of tiagabine, leading to a clinically significant change in clearance. For this reason, a specific drug-drug interaction study is not planned.

Gabapentin:

Gabapentin has a similar disposition to pregabalin in terms of low protein binding (<3%) and high renal clearance. Healthy volunteer studies with common AEDs which are known to induce or inhibit 3A and UGT metabolism had no effect on the clearance of gabapentin. Furthermore, pharmacokinetic analysis of gabapentin in patients receiving gabapentin for at least 3 months, on a range of doses of 400-4000 mg/day, revealed that coadministration with lamotrigine had little or no effect on gabapentin concentrations and these were higher than the gabapentin concentration range observed when coadministered with phenytoin, carbamazepine and valproate [May et al., 1997]. In terms of the effects of gabapentin on the clearance of lamotrigine, a recent retrospective review article of the effect of antiepileptic drugs on the clearance of lamotrigine was investigated in a retrospective analysis, using the data from 570 medical charts of outpatients with epilepsy (≥ 12 years) [Weintraub et al., 2005]. They reported the mean clearance to be between 93 and 97% of the monotherapy value when coadministered with gabapentin, with the ratios being based on both within and between patient comparisons. The mean clearance in patients (N=34) taking lamotrigine alone was reported to be 39.9 ml/h/Kg versus 38.9 ml/h/Kg when coadministered with gabapentin in the same patients. Between patient comparisons were also made based on data from 97 patients. The mean clearance of lamotrigine monotherapy was 43.2 ml/h/kg (n=409), and in a separate group of patients taking lamotrigine in combination with gabapentin was 40 ml/min/kg (n=97). Therefore, the likelihood of either lamotrigine causing inhibition or induction of the clearance of gabapentin or gabapentin inducing or inhibiting the clearance of lamotrigine is minimal.

In conclusion, the probability of a drug interaction between LAMICTAL and gabapentin is considered minimal and would likely not be clinically significant. Proposed labeling for LAMICTAL includes a summary of the published information by Weintraub et al.

Pregabalin:
The prescribing information for pregabalin states that "steady-state trough plasma concentrations of lamotrigine were not affected by concomitant pregabalin (200 mg three times a day) administration." It also reports that lamotrigine has no effect on the pharmacokinetics of pregabalin.

GSK will incorporate this information verbatim into proposed labeling for LAMICTAL.

OCP comments:

1. The Sponsor's response regarding the PK drug-drug interaction potential involving coadministration of tiagabine or gabapentin seems reasonable from a clinical pharmacology and biopharmaceutics perspective. The references provided by the Sponsor and this reviewer's own literature review support the Sponsor's justification for not conducting specific drug-drug interaction studies at this point, since clinically relevant PK interactions are unlikely for these combined medications. The Sponsor's argument for not conducting additional PK interaction studies is justified.

2. Even though the clinically relevant PK interactions are unlikely, pharmacodynamic (PD) interactions, such as enhancement in clinical efficacy, have been reported in

literature for some other newer AEDs without altering the PK profiles. Consequently, the potential PD interaction between lamotrigine and concomitant AEDs, such as tiagabine or gabapentin, cannot be ruled out but is unknown at the point.

3. From a clinical pharmacology and biopharmaceutics perspective, the Sponsor's proposal for pregabalin-related prescribing information in label is acceptable.

Agency Comment 2:
The Agency commented that the recommendation that maintenance doses of LAMICTAL may need to be twice the recommended doses in women receiving oral contraceptives may give rise to clinical scenarios for which tolerability data are not available. In addition, for the conversion to monotherapy setting, the Agency requested that GSK provide guidance in decreasing LAMICTAL to a dose of 500 mg daily for patients on oral contraceptives who may be receiving higher doses. Finally, because of the possibility of increases in lamotrigine levels and adverse events during the "pill-free" week the Agency requested that this phenomenon be more prominently described in labeling.

Sponsor Response:
A summary of the available data on the tolerability of LAMICTAL at doses or dose equivalents greater than 500 mg/day and on the tolerability of LAMICTAL in women who are also taking oral contraceptives is provided in Module 5.3.5.3. The following data sources are summarized:

Tolerability of doses >500mg/day:
- Data from clinical trials US17 and US26, sponsored by GlaxoSmithKline
- Data from a database of epilepsy patients, maintained by the Comprehensive Epilepsy Center at Columbia University, New York, New York

Tolerability of LAMICTAL in women who are also taking an oral contraceptive:
- Data evaluated from the Comprehensive Epilepsy Center at Columbia University
- Data collected from patients in the clinical development program for bipolar disorder

Collectively these sources document an increasing incidence of non-serious CNS adverse events (primarily dizziness and ataxia) with increasing exposure to LAMICTAL. These events have previously been identified as dose-related adverse events associated with the use of LAMICTAL and are non-serious, predictable and easily managed clinically.

These data provide the rationale to support the currently refined dosing recommendations contained within this response for increasing and decreasing the dose of LAMICTAL in situations where the maintenance dose exceeds the current recommended maximum of 500 mg/day and for the use of LAMICTAL in women who are also taking oral contraceptives.

We are also providing GSK's February 2005 response to comments and questions received from the (b) (4) These recommendations are similar to what is being proposed for the US label.

OCP Summary of the data sources:

I. Tolerability for dose > 500 mg/day:

Safety and tolerability of 500 mg/day dosing regimen have been previously established in controlled trials (US05 and US30/31) as adjunctive therapy with enzyme-inducing AEDs. In US05 controlled trial, 500 mg/day monotherapy resulted in average serum concentration of 8.1 μg/mL.

The US17 trial was an open-label continuation study in which lamotrigine doses up to 700 mg/day were studied. The US26 trial was an open-label treatment study in which dosage of lamotrigine was individualized based on age, concomitant AEDs, and clinical response. Serum concentration of 10 μg/mL correlated to 600 mg/day of lamotrigine. The Sponsor reports a linear relationship between the dose and lamotrigine steady-state serum levels at doses up to 700 mg/day. Assuming linear relationship holds true for doses >700 mg/day, the Sponsor projects a serum concentration of 15 μg/mL for a monotherapy 900 mg/day dosing regimen. Based on the data analysis of both trials, the Sponsor reports that exposure in these studies reached 16 μg/mL (corresponding to monotherapy doses to 1000 mg/day). Higher doses with higher incidence of common CNS-related AEs had similar most frequent AE profiles to that of lower doses. There were 9 cases (4%) of SAEs that occurred in patients with levels <10 μg/mL (mean 5.4 μg/mL) and 4 cases (3%) that occurred in patients with levels ≥10 μg/mL (mean 14.7 μg/mL).

II. Columbia database in Publication by Hirsch et al.:

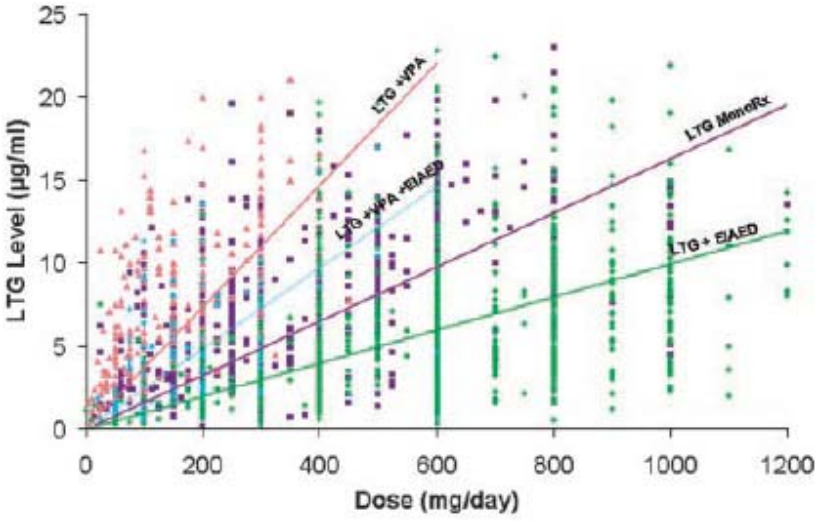
The Sponsor provides the following publication by Hirsch et al., as discussed below, to support a linear relationship between doses and concentrations over a wider dose range for lamotrigine:

Hirsch et al. Correlating lamotrigine serum concentrations with tolerability in patients with epilepsy. *Neurology* 63;1022-1026, 2004.

This study by Hirsch et at. also examined the relationship between clinically reported toxicity and concentrations of lamotrigine (0-4.9, 5-9.9, 10-14.9, 15-19.9, and >20 μg/mL). Hirsch et al. reports that the proportion of patients with toxicity increased with increasing lamotrigine serum concentration, regardless of the type of concomitant AEDs or the use of monotherapy. However, the correlation between lamotrigine levels and tolerability was independent of concomitant medication. Substantial individual variability was found. The authors reported efficacy at therapeutic or target range of 1.5~10 μg/mL, along with incremental benefit in efficacy when at high levels (10~20 μg/mL) which was reported to often be tolerated well. The correlation of serum levels and toxicity and seizure-free for 6-months (efficacy measure) is shown in the following table:

Lamotrigine Serum Concentrations	Corresponding Doses (mg/day)	% of Regimens Toxic	% of Patients Toxic	Seizure-free for ≥6 months
<5 μg/mL	<300	4.3% (n = 975)	7.1% (n = 462)	42.9% (n = 112/261)
5 ~ 9.9 μg/mL	300 ~ 600	7.7% (n =1024)	14.3% (n = 460)	41.2% (n = 121/294)
10 ~ 14.9 μg/mL	600 ~ 900	15.9% (n = 421)	24.2% (n = 231)	40.1% (n = 65/162)
15 ~ 19.9 μg/mL	900 ~ 1200	26.7% (n = 105)	33.8% (n = 71)	29.1% (n = 16/55)
>20 μg/mL	>1200	52.4% (n = 21)	59% (n = 17)	14.3% (n = 2/14)

The most common side effects were CNS-related imbalance, dizziness, and drowsiness. Overall (238/570, 42%) of patients achieved a ≥6 months of seizure freedom. The potential benefit of higher lamotrigine levels was demonstrated in the seizure-free rates which showed some incremental benefit up to >20 μg/mL, where 29% of patients with levels of 15 to 20 μg/mL achieved seizure freedom for ≥6 months. The updated results from the Columbia database show that 267 out of 1284 patients (~25%) had lamotrigine concentrations in the range of 10~14.9 μg/mL (600~900 mg/day) from doses based on clinical response, with 26.5% of them experiencing AEs attributed to lamotrigine. The relationship between lamotrigine concentrations and doses, with or without concomitant AEDs is shown in the following plot:



No detail of formal assessment for dose-proportionality is available in this report. Based on visual examination of the plot above, there seems to be a dose-linear relationship for lamotrigine serum levels up to 1000 mg/day as monotherapy, with some reaching greater than 20 µg/mL at 800 mg/day. Of note, the serum levels obtained from patients who took doses greater than 800 mg/day seem to be slightly lower.

III. Oral contraceptives:

This was a retrospective analysis of safety data of lamotrigine monotherapy in women with bipolar disorder who also received OC during the studies. The Sponsor reports that there is a lack of signal for OC use and a clinically meaningful increase in commonly occurring AEs. The AEs observed were of typical lamotrigine dose-related CNS adverse events and were not attributed to the interaction between OC and lamotrigine.

OCP comments:

1. Even though there is a lack of information in literature on the dose-proportionality of lamotrigine at higher doses, the reference provided by the Sponsor seems to support an apparent dose-linear relationship for lamotrigine up to 1000 mg/day as monotherapy.

2. The Sponsor's rationale and justifications for adjusting the dose of lamotrigine in women taking concomitant oral contraceptives (i.e., combined oral contraceptives as indicated in the Sponsor's response to (b) (4)) are reasonable from an OCP perspective. On the basis of exposure comparison, the increase of the maintenance doses of lamotrigine up to 2-fold (800~1000 mg/day) in the absence of enzyme-inducing AEDs for female patients while on hormonal oral contraceptives will likely result in exposure comparable to or no higher than that of maximum recommended 500 mg/day doses. The Sponsor's proposal for dose adjustments is acceptable from a PK standpoint. However, this does not address the pill free week and the safety of higher concentrations should be assessed by the Medical Officer.

3. The proposed dose adjustment up to 2-fold would be valid under the circumstance in which the patients are on ethinylestradiol (or EE)-containing combined OC, since ethinylestradiol has been reported in a three-arm, open, prospective trial to be the component that induced the glucuronidation (or clearance) of lamotrigine up to 2-fold and hence alter the PK of lamotrigine. Progestogens-containing OCs (e.g., Progestin Only Pills (POPs)), on the other hand, were reported not to affect the exposure-to-dose ratios of lamotrigine. [A. Reimers et al. *Epilepsia.* 46:1414-1417, 2005]. Dose adjustments up to twice the recommended doses when taking these non-EE-containing OC preparations will likely result in much higher exposure and hence potential dose-related AEs. Therefore, caution should be taken when considering adjustments for dosage of lamotrigine in women who are taking different types of hormonal OC, other than combined OC. It will be helpful to monitor the plasma lamotrigine levels and adjust the dose individually to maintain therapeutic levels for seizure control.

4. The tolerability data presented by the Sponsor seem to suggest tolerability across a wide range of lamotrigine concentrations, such as 3~14 μg/mL. Literature information also seem to suggest a wide range of serum concentration that is associated with clinical efficacy of lamotrigine. However, this safety assessment can only be made by the Medical Officer.

1.3. PROPOSED LABELING CHANGES

The Sponsor has proposed changes to the labeling for Lamictal® (based on the version in AE Letter dated Dec. 7, 2005) for the "Drug Interaction", "Hepatic Disease", and "Race" under "CLINICAL PHARMACOLOGY", "Monotherapy Use" under "INDICATION AND USAGE", "Concomitant Use with Oral Contraceptives" and "Drug Interactions" under "PRECAUTIONS", "Epilepsy: Monotherapy Use" and "Special Populations" under "DOSAGE AND ADMINISTRATION", and "PATIENT INFORMATION LEAFLET". The proposed revisions, along with Sponsor's justifications for Race and Patients with Hepatic Impairment, are provided as follows:

CLINICAL PAHRMACOLOGY

"Drug Interactions" under "PRECAUTIONS"

Drug Interactions: As requested by the Agency, information regarding felbamate, gabapentin, pregabalin, topiramate, and zonisamide has been added.

Hepatic Disease: GSK has adopted wording for this section as provided in the Agency's December 3, 2002 approvable letter for NDA 20-241/S-0101 and NDA 20-764/S-003.

Race: The Agency noted that in its analysis of LAM40097, black patients had trough plasma concentrations at week 19 that were 79% higher than Hispanic patients and 41% higher than white patients. The agency asked that GSK address this finding in

light of current labeling which states that the apparent clearance for lamotrigine was 25% lower in non-Caucasians than Caucasians.

While the observation that the mean lamotrigine trough concentrations at week 19 or 24 are 79% higher than Hispanic patients and 41% higher than white patients is correct, these concentration data must be considered in the light of concomitant medications as, for all groups, higher lamotrigine concentrations were observed with concomitant VPA than with either of the other dosing groups. Among black patients 5/7 or 71% were taking concomitant VPA while only 36% and 46% of Hispanic and White patients respectively were taking concomitant VPA. The mean lamotrigine concentration for black patients taking concomitant VPA was 7.2 mcg/ml (n=5) compared with 6.8 mcg/ml for White patients (n=11) and 5.2 mcg/ml for Hispanic patients (n=5). The other two Black patients were both taking concomitant enzyme inducing AEDs and had a mean concentration of 4.9 mcg/ml which was higher than the Hispanic (n=8, 2.6 mcg/ml) or the White (n=10, 2.7 mcg/ml) patients. However one of the two Black patients had a concentration of 1.5 mcg/ml while the other had a concentration of 8.5 mcg/ml. GSK believes the differences in the number of patients using concomitant VPA across these racial groups accounts for most of the difference in lamotrigine serum concentrations observed in this study.

In contrast, the wording in current labeling is based on a population pharmacokinetic analysis of patients who participated in Phase 2 and Phase 3 clinical trials of LAMICTAL during the original clinical development program (report submitted to NDA 20-241 on May 25, 1993). Because this analysis included patients from multiple studies, GSK believes this is a more appropriate reflection of the effect of race on lamotrigine clearance. For this reason, we propose maintaining the current wording.

OCP comments:

1. The currently approved label states that "The apparent oral clearance of lamotrigine was 25% lower in non-Caucasians than Caucasians." The Sponsor's rationale for retaining the current wording based on a population PK analysis pooling data from multiple clinical trials seems reasonable and is acceptable from an OCP perspective.

2. The Sponsor attributes the findings of much higher trough levels in patients who are Black (than those of Hispanic and White) to the potential metabolic inhibition by concomitant valproate or enzyme-inducing AEDs in some subjects. While this is a plausible explanation, it is this reviewer's view that the potential polymorphic and/or ethnic differences in N-glucuronidation and differential induction of the metabolic enzyme cannot be ruled out and may have contributed in part to the interindividual variability in PK parameters, such as CL and exposure. Even though no investigation has been conducted for lamotrigine, polymorphic and ethnic differences have been reported for the N-glucuronidation of other UGT1A4 substrates, such as nicotine.

(b) (4)

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(4

PRECAUTIONS

Concomitant Use with Oral Contraceptives: New subsection advising clinicians about the possible need for dosage adjustments and the possible occurrence of adverse events during the "pill-free" week adverse events has been added at the Agency's request.

Drug Interactions: Information regarding the interaction of lamotrigine with felbamate, gabapentin, pregabalin, topiramate, and zonisamide has been added at the Agency's request. Table 3 of labeling has been revised to incorporate this additional information.

(b) (4)

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(4

Special Populations: Women and Oral Contraceptives: At the Agency's request, this subsection has been revised to provide more specific information on increasing the maintenance dose of LAMICTAL in women also receiving oral contraceptives, guidance on adjustments to the maintenance dose during the pill-free week in cases where adverse events occur consistently during this period, and guidance on decreasing the maintenance dose of LAMICTAL in women stopping oral contraceptives.

Special Populations: Patients with Hepatic Impairment: GSK has adopted the categories of impairment noted in the Agency's December 3, 2002 approvable letter. However, GSK believes that the (b) (4) proposed in NDA 20-241/S-010 and NDA 20-764/S-003 is appropriate. A justification for maintaining these guidelines is provided in Attachment 2. (see below)

Attachment 2 included in submission:
This document is provided by the Sponsor in response to December 3, 2002 Approvable Letter in which the Agency requested that the Sponsor incorporates of the following wording in a "Special Supplement-Changes Being Effected" supplement submitted by the Sponsor on February 8, 1999:

CLINICAL PHARMACOLOGY – Hepatic Disease

The pharmacokinetics of lamotrigine following a single 100-mg dose of LAMICTAL were evaluated in 24 subjects with mild, moderate, and severe hepatic dysfunction (Child-Pugh Classification system) and compared with 12 subjects without hepatic impairment. The patients with severe hepatic impairment were without ascites (n = 2)

or with ascites (n = 5). The mean apparent clearance of lamotrigine in patients with mild (n = 12), moderate (n = 5), severe without ascites (n = 2), and severe with ascites (n = 5) liver impairment was 0.30 ± 0.09, 0.24 ± 0.1, 0.21 ± 0.04, and 0.15 ± 0.09 mL/min/kg, respectively, as compared to 0.37 ± 0.1 mL/min/kg in the healthy controls. Mean half-life of lamotrigine in patients with mild, moderate, severe without ascites, and severe with ascites liver impairment was 46 ± 20, 72 ± 44, 67 ± 11, and 100 ± 48 hours, respectively, as compared to 33 ± 7 hours in healthy controls.

DOSAGE AND ADMINISTRATION – Patients with Hepatic Impairment
Experience in patients with hepatic impairment is limited. Based on a clinical pharmacology study in 24 patients with mild, moderate, and severe liver dysfunction (see CLINICAL PHARMACOLOGY), the following general recommendations can be made. No dosage adjustment is needed in patients with mild liver impairment. Initial, escalation, and maintenance doses should generally be reduced by approximately 25% in patients with moderate and severe liver impairment without ascites and 50% in patients with severe liver impairment with ascites. Escalation and maintenance doses may be adjusted according to clinical response.

The Sponsor agrees to the Agency's recommendation for the above changes in labeling language to the "CLINICAL PHARMACOLOGY – Hepatic Disease" section. However, the Sponsor continues to believe that (b) (4)

(b) (4)

(b) (4)

OCP comments:

1. (b) (4)

2. (b) (4)

PATIENT INFORMATION LEAFLET

Addition of possible side effects that could occur when oral contraceptives are started and stopped in patients receiving concomitant LAMICTAL and oral contraceptives.

1.4. RECOMMENDATIONS

The Office of Clinical Pharmacology has reviewed the current submission, including the final proposed labeling for Lamictal® Tablets and Chewable Dispersible Tablets. The OCP finds this submission acceptable provided that outstanding labeling issues are adequately resolved from a clinical pharmacology and biopharmaceutics perspective.

From an OCP perspective, the Sponsor has provided compelling argument to the OCP comment regarding drug-drug interactions between lamotrigine and tiagabine, gabapentin, and pregabalin, and the responses are acceptable. The proposed revisions for labeling languages pertinent to drug-drug interactions and Special Population are acceptable. The justifications for retaining labeling language for race and (b) (4) seem reasonable. The proposed dose adjustments in women taking combined hormonal contraceptives may be reasonable and the Medical Officer will be assess this in more detail. However, consideration should be taken for circumstances (and pertinent labeling languages) in which increasing lamotrigine dose may not be appropriate for women who are taking different oral contraceptive preparations which do not alter the clearance or exposure of lamotrigine.

The OCP recommendations and labeling comments should be conveyed to the Sponsor as appropriate.

2. LABELING RECOMMENDATIONS

The Office of Clinical Pharmacology has reviewed the proposed labeling, with focus on the specific sections highlighted in Section 1.3., for Lamictal®, and found it acceptable provided that revision is made to the labeling language.

Labeling recommendation to be sent to the Sponsor:
The proposed changes made by the Sponsor are in **RED underlined and ~~strikethrough~~ text**. The proposed changes made by the OCP to the label language are in **RED text** with yellow-highlight: the **underlined text** is the proposed change and the **~~strikethrough~~ text** is recommendation for deletion from an OCP perspective.

Ta-Chen Wu, Ph.D.
Reviewer, Neurology Drug Products, DCP-1, OCP

Concurrence: Ramana S. Uppoor, Ph.D.
Team Leader, Neurology Drug Products, DCP-1, OCP

Cc: HFD-120 NDA 20-241, 20-764
CSO/C. Calder
/TL Clin Pharm/R. Uppoor
HFD-860 /DD DCP-1/M. Mehta

52 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

___X___ Draft Labeling (b4)

___X___ Draft Labeling (b5)

_____ Deliberative Process (b5)

_____ Law Enforcement Action (b7)

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Ramana S. Uppoor
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BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW
DRUG: Lamictal® (Lamotrigine) PRIMARY REVIEWER: Andre Jackson

NDA: 20241 -Tablets
NDA: 20764-Chewable Tablets

TYPE: NDA

STRENGTH: 25mg, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg

APPLICANT: GSK

Submission Dates: February 4, 2005
June 29, 2004
August 11,2004

INDICATIONS: Primary Generalized Tonic –Clonic Seizures

EXECUTIVE SUMMARY

SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The firm has a submitted a supplemental application seeking approval of Lamictal as adjunctive treatment of primary generalized tonic-clonic seizures (PGTC) in pediatric and adult patients. Lamictal is currently approved for adjunctive therapy in Pediatric Patients with Partial Seizures and Adjunctive Therapy in Pediatric and Adult Patients With Lennox-Gastaut Syndrome. Lamictal is also indicated for conversion to monotherapy in adults.

The firm is (b) (4)

The firm conducted a trial Study LAM 40097 consisting of a Screen and three Phases (i.e., Baseline, dose Escalation, Maintenance) that lasted 32 weeks for subjects who were 2-12 years of age, and lasted 27 weeks for subjects who were >12 years of age. The reason for these differing lengths was that the Escalation Phase for subjects aged 2-12 years was longer than that for subjects >12 years of age. Concurrent therapies during the study consisted of valproic acid with or without another AED, inducing AEDs (phenytoin etc), other AEDs. Results from the study did not show any major differences in Lamictal trough concentrations as a result of the combination therapy. The average maintenance doses (i.e.,199 mg and 215 mg) were 35% lower for Hispanic and Black females compared to whites(307 mg), which was statistically significant. Other subgroups and AED treatment groups did not exhibit any significant interactions related to age, sex, ethnic origin and dosing regimen that affected either the Lamotrigine trough plasma levels or lamictal dosing when lamotrigine was used as adjunctive therapy with other AEDs.

(b) (4)

PLEASE FORWARD THE LABELING COMMENTS TO THE SPONSOR.

The proposed re-organization of the label is acceptable to OCPB.

COMMENTS TO THE MEDICAL OFFICER/PROJECT MANAGER

The firm has not supplied any supportive data for Tiagabine and for Gabapentin as interacting drugs with Lamictal. For tiagabine there may be reason for concern since it is recommended that it be withdrawn slowly which may have some pharmacokinetic or effectiveness implications in conversion to monotherapy with lamictal. On the other hand, gabapentin is renally excreted so it is unlikely to interact however, there is no experimental data on its interaction with lamictal.

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QUESTION BASED REVIEW

Are there any Pharmacokinetic factors related to age, gender or race that would preclude Lamotrigine being used as adjunctive therapy in primary generalized tonic clonic (PGTC) seizures in children and adults?

The firm conducted a trial consisting of a Screen and three Phases (i.e., Baseline, dose Escalation, Maintenance) that lasted 32 weeks for subjects who were 2-12 years of age, and lasted 27 weeks for subjects who were >12 years of age. The reason for these differing lengths was that the Escalation Phase for subjects aged 2-12 years was longer than that for subjects >12 years of age. The other AED's studied were divalproex, zonisamide, sodium valproate, topiramate, phenytoin, phenobarbital, clobazem, gabapentin, ethosuximide, clonazepam, carbamazepine and levetiracetam. The phases of the trial were:

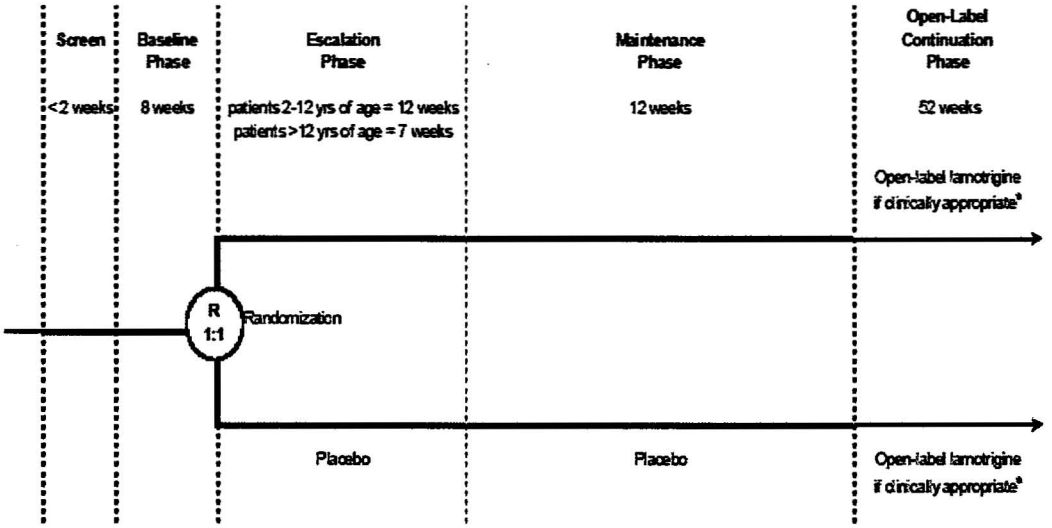
• Baseline Phase (8 weeks);
Baseline assessment of PGTC seizures was prospective, historical, or a combination of these two. With authorization from the Sponsor subjects with reliable documentation of their seizures were able to use 1) a historical Baseline Phase totaling 8 consecutive weeks; or 2) a combination of the historical baseline and prospective baseline totaling 8 consecutive weeks prior to randomization.

• Escalation Phase (12 weeks for subjects 2-12 years of age, and 7 weeks for subjects >12 years of age);

• Maintenance Phase (12 weeks).
Two Time and Events schedules are provided for subjects 2-12 years of age and subjects >12 years of age . In these schedules, the term Treatment Phase is used to refer to the Escalation Phase and the Maintenance Phase

The study design is summarized in Figure 1, "Study Design."

Figure 1 Study Design



Summary of Lamotrigine Trough Serum Concentrations (ng/mL): Subjects 2-12 years of age

Treatment	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Lamictal	Vis 1/Scrn	8	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	11	2101.7	1362.6	2021.3	217.9	4755.9
	Vis 6/Wk 11	9	5081.5	3074.6	4448.7	809.6	11308.6
	Vis8or9/Wk19or24	8	5081.2	2679.9	3855.5	2450.5	9980.8
	Early WD	2	2570.6	398.2	2570.6	2289.1	2852.2
Placebo	Vis 1/Scrn	7	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	9	0.0	0.0	0.0	0.0	0.0
	Vis 6/Wk 11	8	0.6	1.8	0.0	0.0	5.1
	Vis8or9/Wk19or24	7	9.7	25.7	0.0	0.0	68.0
	Early WD	1	0.0		0.0	0.0	0.0

Summary of Lamotrigine Trough Serum Concentrations (ng/mL): Subjects > 12 years of age

Treatment	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Lamictal	Vis 1/Scrn	26	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	29	4026.1	2790.1	3386.4	817.6	13768.3
	Vis 6/Wk 11	30	5401.5	3556.5	4666.7	1360.9	14513.9
	Vis8or9/Wk19or24	30	4558.2	3369.4	3530.9	83.2	13592.9
	Early WD	5	4727.8	4866.5	2196.2	970.6	12361.1
Placebo	Vis 1/Scrn	26	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	31	0.0	0.0	0.0	0.0	0.0
	Vis 6/Wk 11	23	0.0	0.0	0.0	0.0	0.0
	Vis8or9/Wk19or24	20	241.4	1019.7	0.0	0.0	4566.7
	Early WD	4	1115.3	2230.6	0.0	0.0	4461.1

The plasma concentrations observed in the 2-12 yr old and 12 years and above age groups were similar despite the concomitant medication except for visit 5 where the <12 yr old group's levels were one-half the >12 yr old group. Graphs for each of the following parameters (i.e., number of seizures, lamictal concentration total escalation dose, age, maintenance dose, escalation average dose and total daily dose exhibited no correlations for each AED investigated despite the AED present. Half of the subjects in the lamotrigine treatment group took one AED; half took two AEDs. In the placebo treatment group, 59% of subjects took one AED; 41% took two AEDs.

The average maintenance doses were 35% lower for Hispanic and Black females compared to whites which were statistically significant. There were no other noteworthy differences in either trough plasma levels or dose requirements for lamictal when it was used as adjunctive therapy with the other AEDs investigated.

SUMMARY COMMENTS

1.2-12 yrs had slightly higher mean (11%) trough plasma concentrations ng/ml at wk 19 than those >12 yrs old (ie 5081 vs 4558).

2. Females had a higher (30%) mean trough plasma concentration ng/ml at wk 19 or 24 than males (ie 5297 vs 4102).

3. Blacks had higher mean trough plasma concentrations ng/ml at wk 19 or 24 than Whites or Hispanics(ie 6564 vs 4656 and 3664). Blacks trough plasma concentrations ng/ml at wk 19 or 24 were 79% higher than Hispanics and 41% higher than Whites.

4. There was no relationship between age and lamotrigine mean trough serum levels ng/ml for subjects taking valproic acid (6983-2 to 12 and 6963 >12 yrs of age).

5. The mean lamotrigine trough serum levels ng/ml for subjects on other EIAED regimens were similar at wk 19 or 24 for younger subjects (3052-2 to12 yrs and 2908 >12 yrs of age).

6. There was no relationship between age and lamotrigine mean trough serum levels ng/ml for subjects taking "other AEDs" (3557-2 to12 and 3321 >12 yrs of age).

7. There was no relationship between age and lamotrigine mean trough serum levels ng/ml for subjects taking " VPA alone" (5984-2 to12 yrs and 6448 >12 yrs of age).

8. Younger subjects 2-12 taking VPA plus non-inducers had higher lamotrigine mean trough serum levels 9980 ng/ml than did older subjects >12 yrs ,8008 ng/ml. The levels were 25% higher.

9.The only statistically significant findings were related to ethnic origin black vs white (hispanics were not included in the study population) for subjects on Divalproex that received adjunct Lamictal. There was a significant statistical difference between blacks and whites for the **total** maintenance dose in these subjects 16292 mg vs 7086 mg at the end of 12 weeks.

10. The labeling changes proposed by the firm are in agreement with the current in-use label which is being listed and is the FDA version of the label in the PDR. The firm has supplied data to support the new information in the label.

DRUG DRUG INTERACTIONS –SEE ALSO APPENDICES III-VI

- Lamotrigine- AUC and Cmax decreased by about 10% in the presence of Topiramate
- Topiramate AUC and Cmax values increased 15% in the presence of Lamotrigine.
- There was no effect of oxcarbazepine on lamotrigine or lamotrigine on oxcarbazepine.
- Olanzapine 5-15 mg day resulted in lamotrigine AUC and CMAX to decrease 24% and 20% respectively however, lamotrigine had no effect on Olanzapine.
- No effect of Levetiracetam on lamotrigine and lamotrigine had no effect on Levetiracetam.
- Zonisamide had no effect on lamotrigine but the effect of lamotrigine on zonisamide was not studied.
- Lamotrigine had a minimal effect on ethinyloestradiol PK. Lamotrigine caused a 19% and 12% decrease in AUC(0-24 hr) and Cmax respectively for levonogestrel. 30 mg ethinyloestradiol and 150 mg levonogestrel increased the apparent clearance of lamotrigine by approximately 2-fold with a mean decrease in AUC of 52% and 39% for Cmax.

Are there any Pharmacokinetic reasons that conversion to the mono-therapy indication from adjunctive therapy in adults should be restricted to only valproate, phenytoin, carbamazepine, primidone, and phenobarbital?

Table 1. Synopsis of references on Lamictal drug interactions related to conversion from adjunct to mono-therapy.

STUDY DESIGN	Potential affect on Lamictal	STUDY DESIGN	Lamictal affect on the Drug	Comments
N 24 DOSES –mg/day 50-800 TPM 150-950 LTG STUDY LENGTH Study 1-23 mos. DESIGN Taking LTG & other AEDs TPM given SAMP SCHED 1.Prior to TPM dose-AED measured 2.CMIN 3.Prior to dose escalation 4.While TPM given	Ref 1 Berry et. al. **TOPERIMATE(TPM)** ANOVA for ratio TPM on LTG MEAN CONC=0.942, 90% CI(89-99)	**N 13** DOSES – MG/DAY 300-400 LTG&TPM STUDY LENGTH Study 1-23 mos. DESIGN LTG-mono-2 wks Stable LTG w/inc TPM combined with decreased LTG 4 wks Stable TPM 2 wks SAMP SCHED Throughout the study	**Ref 7-Dose** TPM **SS study for 16 weeks** **No effect OF LTG**	*Based upon Toperimate label* 5 (a)Lamotrigine- AUC and Cmax decreased by about10% in the presence of Topiramate 5(b) Topiramate –15% increase in AUC and Cmax in the presence of Lamotrigine ***Conclusions:*** **TPM did not cause a significant change in LTG serum concentration in this group of patients. Key Words:**
N=21	**Ref 5-Felbamate**			

DOSES –mg/day LTG 50-100 mg/12 hrs FEL-600-1200 mg/12hrs STUDY LENGTH 2 10-day periods DESIGN Both given together SAMP SCHED 1. CMIN from day 10 2. Intense 0-12 hr after morning dose daya 10	**Colucci et al** **10 day study at ss** Cmax and AUC(0-12) 13% and 14% higher w/felbamate 90% CI (106-120%) (108-121%) Ref 8-Felbamate Gidal et al			
N=21 DOSES Oxcarbazepine-300mg-600 mg bid Lamotrigine-25mg/day-200 mg/day SAMP SCHED Days 51-52 prior to morning dose with a 0-24hr profile on day 53	**REF 9-CBE submitted to FDA June 2004** Lamotrigine AUC and CMAX 8% AND 2% lower with oxcarbazepine		Oxcarbazepine AUC AND CMAX 6% and 4% lower	There appeared to be no effect of oxcarbazepine on lamotrigine or for lamotrigine on oxcarbazepine
N=17, 12, 17 DOSES LTG titrated to 200 mg by day 47 Olanzapine 5-15 mg day	**REF 30-CBE submitted to FDA June 2004** Lamotrigine AUC and CMAX 24% and 20% lower with Olanzapine	Same	Lamotrigine has no effect on Olanzapine	

43-47 DESIGN Cohort 1-LTG & Olanzapine Cohort 2-LTG & Placebo Cohort 3-Placebo& Olanzapine SAMP SCHED PK profile on Day 56 over 24 hrs				
N=16 DOSES Not given SAMP SCHED Not given	**REF 12-**.Hachad H, et.al. **REVIEW ARTICLE** METHOSUXIMIDE lowers LTG levels in patients w/deterioration in seizure control		No effects reported	Not regularly prescribed so firm did not include in label.
	PDR- Levetiracetam had no effect on Lamotrigine		Lamotrigine had no effect on Levetiracetam	
DOSES Not given SAMP SCHED Not given	[redacted] (b) (4)			
DOSES Zonisamide 100mg/day DESIGN Titration to 200 mg/day	Reference 23-Schellenberger et.al. Zonisamide Zonisamide no effect on		LTG effect on zonisamide not studied	

SAMP SCHED Day 35	LTG			
	REF 12-.Hachad H, et.al. **REVIEW ARTICLE** Gabapentin is not metabolized and excreted in the urine			No info in PDR This will have to be addressed by the MO and the firm. Drug is renally excreted so it is unlikely it interacts but no experimental data.

Other AEDs such as clobazam, clonazeopam, primidone, vigabatrin, felbamate are not important clinically so their potential for drug-drug interaction was not considered by the firm. I also discussed these with Dr. Sheridan who supported the fact that these were of minor importance. All of the AED's listed in the current Table show no interaction with lamotrigine. For gabapentin and tiagabine, additional information will be required on these drugs.

Sponsor's Proposed Guidelines for Conversion of Adults with Partial Seizures Receiving AEDs

As with the currently approved guidelines for converting adult patients receiving CBZ, PHT, PB, PRM or VPA to monotherapy with LAMICTAL, (b) (4)

(b) (4)

BACKGROUND
Pharmacokinetics

Adults

Lamotrigine is rapidly and completely absorbed after oral administration with negligible first-pass metabolism (absolute bioavailability is 98%). The bioavailability is not affected by food. Peak plasma concentrations occur from 1.4 to 4.8 hours in healthy volunteers or patients with epilepsy following single or multiple administration. Estimates of the mean apparent volume of distribution (Vd/F) of lamotrigine following oral administration ranged from 0.9 to 1.3 L/kg. Vd/F is independent of dose and is similar following single and multiple doses in both patients with epilepsy and in healthy volunteers.

Data from *in vitro* studies indicate that lamotrigine is approximately 55% bound to human plasma proteins at plasma lamotrigine concentrations from 1 to 10 µg/mL. Because lamotrigine is not highly bound to plasma proteins, clinically significant interactions with other drugs through competition for protein binding sites are unlikely. The binding of lamotrigine to plasma proteins did not change in the presence of therapeutic concentrations of PHT, PB (PB), or VPA. Lamotrigine at therapeutic concentrations did not displace other AEDs (CBZ, PHT, PB) from protein binding sites. Lamotrigine is metabolized predominantly by glucuronic acid conjugation; the major metabolite is an inactive 2-N-glucoronide conjugate. After oral adminstration of 240 mg ^{14}C-lamotrigine (15 µCi) to six healthy volunteers, 94% of the administered dose was recovered in the urine and 2% was recovered in the feces. The radioactivity in the urine consisted of unchanged lamotrigine (10%), the 2-N-glucoronide (76%), a 5-N-glucoronide (10%), a 2-N-methyl metabolite (0.14%), and other unidentified minor metabolites (4%).

Estimates of mean apparent plasma clearance (CL/F) and plasma half-life ($t_{1/2}$) in epileptic patients taking CBZ, PB, PHT, or PRM, the enzyme inhibitor VPA or both were 1.10, 0.28 or 0.53 mL/min/kg and 14.4, 58.8 or 27.2 hours, respectively. Therefore the elimination of lamotrigine in epileptic patients is dependent on the concomitant medication.

Following multiple doses (150 mg bid) to normal volunteers taking no other medications, lamotrigine induced its own metabolism resulting in a 25% decrease in $t_{1/2}$ and a 37% increase in CL/F at steady state compared to values obtained in the same volunteers following a single dose. Evidence gathered from other sources suggests that self induction by lamotrigine does not occur when lamotrigine is given as add-on therapy in patients receiving CBZ, PB, PHT, or PRM.

In healthy volunteers not receiving any other medications and given single doses, the plasma concentrations of lamotrigine increased in direct proportion to the dose

administered over the range of 50 to 400 mg. In two small studies (n=7 and 8) of patients with epilepsy who were maintained on other AEDs, there also was a linear relationship between dose and lamotrigine plasma concentrations at steady state following doses of 50 mg to 350 mg bid.

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

In a single dose study (150 mg LAMICTAL), the pharmacokinetics of lamotrigine in twelve elderly volunteers between the ages of 65 and 76 years (mean creatinine clearance = 61 mL/min; range = 33 to 108) were similar to those of young healthy volunteers in other studies. The clearance of lamotrigine was not affected by gender. The apparent oral clearance of lamotrigine was 25% lower in noncaucasians than Caucasians.

Pediatrics

The pharmacokinetics of lamotrigine following a single 2 mg/kg dose were evaluated in 2 studies of pediatric patients (n = 29 for patients aged 10 months to 5.9 years and n = 26 for patients aged 5 to 11 years). Forty-three patients received concomitant therapy with other AEDs and 12 patients received LAMICTAL as monotherapy.
Population pharmacokinetic analyses involving patients aged 2 to 18 years demonstrated that lamotrigine clearance was influenced predominantly by total body weight and concurrent AED therapy. The oral clearance of lamotrigine was higher, on a body weight basis, in pediatric patients than in adults. Weight-normalized lamotrigine clearance was higher in those subjects weighing less than 30 kg, compared with those weighing greater than 30 kg. Accordingly, patients weighing less than 30 kg may need an increase of as much as 50% in maintenance doses, based on clinical response, as compared with subjects weighing more than 30 kg being administered the same AEDs. These analyses also revealed that, after accounting for body weight, lamotrigine clearance was not significantly influenced by age. Thus, the same weight-adjusted doses should be administered to children irrespective of differences in age. Concomitant AEDs which influence lamotrigine clearance in adults were found to have similar effects in children.

Drug Interactions

Drug-drug interactions were evaluated in NDA 20-241, which presented data on 3015 patients and volunteers to demonstrate the safety and efficacy of LAMICTAL in adult patients with partial seizures. The presence of LAMICTAL does not alter the plasma

concentrations of concomitant AEDs; however, concomitant AEDs do alter the plasma concentrations of lamotrigine. Drugs that induce hepatic drug-metabolizing enzymes (for example, PHT and CBZ) enhance the elimination of lamotrigine relative to that observed in the absence of these drugs. No consistent changes in lamotrigine plasma concentrations associated with the administration of non-AED concomitant medications were observed. Drug-drug interactions were also evaluated in children and adults with Lennox-Gastaut syndrome in NDA 20-764. Briefly, the presence of LAMICTAL was not found to alter the plasma concentration of CBZ, PHT, VPA or clobazam.
The effect of co-administration of lamotrigine 200 mg once a day and oxcarbazepine (OXC) 600 mg bid has been studied in 47 healthy young male volunteers under steady state conditions. Lamotrigine $AUC_{(0-24)}$ and C_{max} at steady state were comparable when lamotrigine was co-administered with OXC, or placebo. The active 10-monohydroxy metabolite (MHD) of OXC $AUC_{(0-12)}$ and C_{max} at steady state were comparable when OXC was administered with lamotrigine, or placebo. The frequency of adverse events was higher during lamotrigine and OXC combination therapy compared to monotherapy, but the lack of pharmacokinetic interaction supports co-administration when clinically indicated, although clinical monitoring of adverse events and dose adjustment may be necessary. A "Special Supplement: Changes Being Effected" with revisions to the current prescribing information for LAMICTAL which reflects this new information was submitted to NDA 20-241 and NDA 20-764 on 29 Jun 2004.

Potential drug interactions between levetiracetam (LEV) and lamotrigine were assessed by evaluating the serum concentrations of LEV and lamotrigine during placebo controlled clinical studies. These data indicate that LEV does not influence the plasma concentration of lamotrigine and that lamotrigine does not influence the pharmacokinetics of LEV . Revisions to the current prescribing information for LAMICTAL which reflect this information was also part of the submission noted above.

The effect of co-administration of LAMICTAL 300 mg once a day and a combined oral contraceptive (Microgynon 30; ethinyloestradiol 30 µg plus levonorgestrel 150 µg) has been studied in 22 healthy young female volunteers under steady state conditions. The oral contraceptive increased the clearance of lamotrigine by approximately two-fold: steady state $AUC_{(0-24)}$ and C_{max} were, on average, 52% and 39% lower, respectively, in the presence of the oral contraceptive. Trough concentrations of serum lamotrigine gradually increased during the "pill-free" interval of oral contraceptive administration; serum concentrations were approximately two-fold higher at the end of the "pill-free" interval, compared to the end of the 21 day cycle of pill administration. Ethinyloestradiol pharmacokinetics were similar in the presence and absence of lamotrigine; steady state levonorgestrel $AUC_{(0-24)}$ and C_{max} were, on average, 19% and 12% lower, respectively, in the presence of lamotrigine. There was no hormonal evidence of ovulation in any participating subject (as measured by serum progesterone), although there was some evidence of loss of suppression of the hypothalmic-pituitary-ovarian axis (measured by serum follicle stimulating hormone, luteinizing hormone and estradiol).
A "Special Supplement: Changes Being Effected" with revisions to the current prescribing information for LAMICTAL which reflects this new information was submitted to NDA 20-241 and NDA 20-764 on 20 Aug 2004.

The interaction of LAMICTAL with PHT, CBZ, and VPA has been evaluated. LAMICTAL has no appreciable effect on steady-state PHT and CBZ plasma concentration. When LAMICTAL was administered to 18 healthy volunteers receiving VPA, the trough steady-state VPA concentrations in plasma decreased by an average of 25% over a 3-week period, and then stabilized.

Study Rationale

Anecdotal reports and clinical case studies indicate that lamotrigine may be effective and well tolerated in controlling primary generalized tonic clonic (PGTC) seizures. However, this has not been studied other than in active-controlled trials in newly diagnosed subjects. Valproate is commonly used to control this seizure type, but the significant side effects associated with its use often add to the debilitating consequences of this disorder. Topiramate is also approved for this use. To address the need for alternative anti-epileptic drugs (AEDs) to treat this seizure type, GSK conducted a randomized, blinded, placebo-controlled study to assess the efficacy and safety of adjunctive therapy with lamotrigine in the treatment of PGTC seizures.

STUDY OBJECTIVES

Primary Objective

• The primary objective of this study was to assess the efficacy of lamotrigine adjunctive therapy in subjects with PGTC seizures.

Secondary Objectives

The secondary objectives were:

• to evaluate the safety and tolerability of lamotrigine adjunctive therapy in subjects with PGTC seizures;

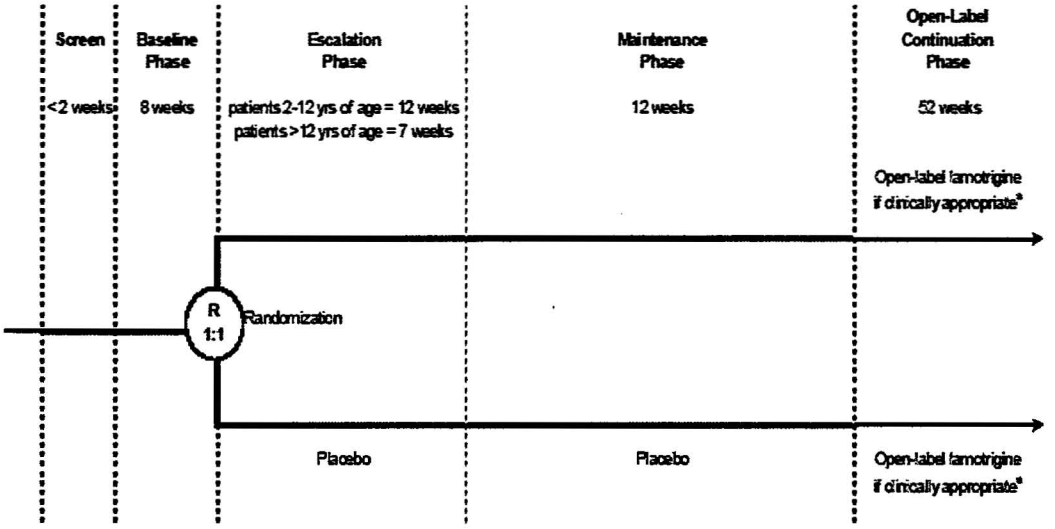
• to evaluate the effect of lamotrigine adjunctive therapy on mood and quality of life in this population;

• to evaluate the effects of lamotrigine adjunctive therapy on body weight in this population.

Study Design

The study design is summarized in Figure 1, "Study Design."

Figure 1 Study Design



The trial consisted of a Screen and three Phases (i.e., Baseline, dose Escalation, Maintenance) that lasted 32 weeks for subjects who were 2-12 years of age, and lasted 27 weeks for subjects who were >12 years of age. The reason for these differing lengths was that the Escalation Phase for subjects aged 2-12 years was longer than that for subjects >12 years of age. The phases of the trial were:

• Baseline Phase (8 weeks);
Baseline assessment of PGTC seizures was prospective, historical, or a combination of these two. With authorization from the Sponsor subjects with reliable documentation of their seizures were able to use 1) a historical Baseline Phase totaling 8 consecutive weeks; or 2) a combination of the historical baseline and prospective baseline totaling 8 consecutive weeks prior to randomization.

• Escalation Phase (12 weeks for subjects 2-12 years of age, and 7 weeks for subjects >12 years of age);

• Maintenance Phase (12 weeks).
Two Time and Events schedules are provided for subjects 2-12 years of age and subjects >12 years of age . In these schedules, the term Treatment Phase is used to refer to the Escalation Phase and the Maintenance Phase.

After completion of all screening procedures, subjects who met the enrollment criteria entered the 8-week Baseline Phase. At the end of the Baseline Phase, subjects who met or exceeded the minimum seizure frequency criteria were randomized in a 1:1 ratio according to a computer-generated randomization schedule to receive either escalating doses of lamotrigine or matching placebo for lamotrigine.

Seizure count was assessed at every clinic visit by review of daily diary, and adverse

events (AEs) and concurrent medications and AEDs were reviewed. Weight and height were recorded at all scheduled visits. Four patient reported outcome questionnaires [the Beck Depression Inventory (BDI-II), the Cornell Dysthymia Rating Scale:Self-Report (CDRS-SR), the Profile of Mood States (POMS), and the Quality of Life in Epilepsy Questionnaire (QOLIE-31)] were administered at Screen and at the end of the treatment period.

Study Medications Product Strength
Lamotrigine 2mg, chewable dispersible tab
Lamotrigine 5mg, chewable dispersible tab
Lamotrigine 25mg, chewable dispersible tab
Lamotrigine 100mg, chewable dispersible tab
Placebo 2mg, chewable dispersible tab
Placebo 5mg, chewable dispersible tab
Placebo 25mg, chewable dispersible tab
Placebo 100mg, chewable dispersible tab

Dosages and Administration

Dosages and Dosing during the Escalation Phase and the Maintenance Phase

After completion of the Baseline Phase, subjects were randomized to receive either lamotrigine or matching placebo for lamotrigine and to enter the Escalation Phase. The duration of the Escalation Phase was 12 weeks for subjects 2-12 years of age, and 7 weeks for subjects >12 year of age.

If randomized to lamotrigine, subjects were assigned to one of 3 dosing schedules depending on their concurrent AED(s):
1. A dosing schedule for subjects taking concurrent valproic acid (VPA) with or without another AED.
2. A dosing schedule for subjects taking a concurrent EIAED (enzyme-inducing antiepileptic drug), with or without another AED other than VPA.
3. A dosing schedule for subjects taking concurrent AED(s) other than VPA and EIAEDs.

For purposes of this study, the major EIAEDs were defined as carbamazepine, phenytoin, phenobarbital and primidone.

The dosing schedules, describing starting doses, target doses, minimum and maximum allowable doses, and dose adjustments are presented in Table 2 and Table 3 .

Table 2. **Lamotrigine Dosing in Subjects 2-12 Years of Age**

	ESCALATION										MAINTENANCE
Concurrent Therapy	Treatment Weeks 1-2	Treatment Weeks 3-4	Treatment Week 5	Treatment Week 6	Treatment Week 7	Treatment Week 8	Treatment Week 9	Treatment Week 10	Treatment Week 11	Treatment Week 12	Treatment Weeks 13-24
Subjects taking VPA (with or without another AED)	0.15 mg/kg/day (1 dose or 2 divided doses)	0.3 mg/kg/day (1 dose or 2 divided doses)	0.6 mg/kg/day (2 divided doses)	0.9 mg/kg/day (2 divided doses)	1.2 mg/kg/day (2 divided doses)	1.5 mg/kg/day (2 divided doses)	1.8 mg/kg/day (2 divided doses)	2.1 mg/kg/day (2 divided doses)	2.4 mg/kg/day (2 divided doses)	2.7 mg/kg/day (2 divided doses)	Target dose: 3mg/kg/day[a] (up to maximum of 200mg/day) (2 divided doses)
Subjects taking an EIAED[d] (with or without another AED other than VPA)	0.6 mg/kg/day (2 divided doses)	1.2 mg/kg/day (2 divided doses)	2.4 mg/kg/day (2 divided doses)	3.6 mg/kg/day (2 divided doses)	4.8 mg/kg/day (2 divided doses)	6 mg/kg/day (2 divided doses)	7.2 mg/kg/day (2 divided doses)	8.4 mg/kg/day (2 divided doses)	9.6 mg/kg/day (2 divided doses)	10.8 mg/kg/day (2 divided doses)	Target dose: 12mg/kg/day[b] (up to a maximum of 400mg/day) (2 divided doses)
Subjects taking AED(s) other than VPA and EIAEDs[d]	0.3 mg/kg/day (1 dose or 2 divided doses)	0.6 mg/kg/day (2 divided doses)	1.2 mg/kg/day (2 divided doses)	1.8 mg/kg/day (2 divided doses)	2.4 mg/kg/day (2 divided doses)	3.0 mg/kg/day (2 divided doses)	3.6 mg/kg/day (2 divided doses)	4.2 mg/kg/day (2 divided doses)	4.8 mg/kg/day (2 divided doses)	5.4 mg/kg/day (2 divided doses)	Target dose: 6mg/kg/day[c] (up to a maximum of 300mg/day) (2 divided doses)

a. If a subject could not tolerate 3mg/kg/day, the dose was decreased to a minimum of 2.25mg/kg/day. If seizure control was inadequate, the dose was increased to 3.75mg/kg/day up to a maximum of 200mg/day.

b. If a subject could not t tolerate 12mg/kg/day, the dose was decreased to a minimum of 9.0mg/kg/day. If seizure control was inadequate, the dose was increased to 15.0mg/kg/day up to a maximum of 400mg/day.

c. If a subject could not tolerate 6mg/kg/day, the dose was decreased to a minimum of 4.5mg/kg/day. If seizure control was inadequate, the dose was increased to 7.5mg/kg/day up to a maximum of 300mg/day.

Table3. Lamotrigine Dosing in Subjects >12 Years of Age

	ESCALATION					MAINTENANCE
Concurrent Therapy	Treatment Weeks 1-2	Treatment Weeks 3-4	Treatment Week 5	Treatment Week 6	Treatment Week 7	Treatment Weeks 8-19
Subjects taking VPA (with or without another AED)	12.5mg/day (given as 25mg every *other* day)	25mg/day (once daily)	50mg/day (2 divided doses)	100mg/day (2 divided doses)	150mg/day (2 divided doses)	Target dose: 200mg/day[a] (2 divided doses)
Subjects taking an EIAED[d] (with or without another AED other than VPA)	50mg/day (2 divided doses)	100mg/day (2 divided doses)	150mg/day (2 divided doses)	200mg/day (2 divided doses)	300mg/day (2 divided doses)	Target dose: 400mg/day[b] (2 divided doses)
Subjects taking AED(s) other than VPA and EIAEDs[d]	25mg/day (once daily)	50mg/day (2 divided doses)	100mg/day (2 divided doses)	150mg/day (2 divided doses)	200mg/day (2 divided doses)	Target dose: 300mg/day[c] (2 divided doses)

a If a subject could not tolerate 200mg/day, the dose was decreased to a minimum of 150mg/day. If seizure control was inadequate, the dose was increased to a maximum of 250mg/day.

b If a subject could not tolerate 400mg/day, the dose was decreased to a minimum of 300mg/day. If seizure control was inadequate, the dose was increased to a maximum of 500mg/day.

c If a subject could not tolerate 300mg/day, the dose was decreased to a minimum of 225mg/day. If seizure control was inadequate, the dose was increased to a maximum of 375mg/day.

d For purposes of this study, the major EIAEDs included carbamazepine, phenytoin, phenobarbital and primidone.

Note: Subjects who did not convert to open-label lamotrigine had their study drug tapered off over at least 2 weeks, by approximately 50% per week, unless safety concerns required a more rapid withdrawal.

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Dosing Guidelines

The following guidelines were followed:

- During the Escalation Phase, dose escalation faster than specified was not permitted. Subjects who could not tolerate the dose escalation were discontinued from the study.
- During the Maintenance Phase, the investigators used their best effort to dose the subjects at the target doses specified. If a subject had unacceptable side effects or inadequate seizure control, the doses of study drug could be increased or decreased as specified in the dosing tables. Subjects who could not tolerate the minimum allowable doses were discontinued from the study.
- If a dose of the study drug was accidentally missed, subjects were instructed to take

the dose as soon as possible, but no later than 4 hours after the scheduled time. If it was more than 4 hours after the scheduled time, the subsequent dose was not increased to make up for the missed dose. Missed doses of the study drug were recorded in the daily diary and transcribed into the Case Report Form (CRF).

Dosages and dosing during the Continuation Phase
Subjects who Completed the Maintenance Phase

After completion of the Maintenance Phase, subjects were offered the opportunity to participate in an open-label Continuation Phase for a long-term follow up and receive open-label lamotrigine, if clinically appropriate, for up to 1 year (i.e., 52 weeks). To maintain the blind, subjects who elected to participate in the open-label Continuation Phase were converted from their blinded study drug to open-label lamotrigine in a double-blind fashion.

When subjects exited the Maintenance Phase and entered the Continuation Phase, they received escalating doses of lamotrigine as outlined in Tables 2 and 3 above, and decreasing doses of blinded study drug, until they were completely off the blinded study drug and receiving an open-label dose of lamotrigine equal to their last blinded Maintenance dose. This process allowed subjects who took blinded lamotrigine during the Escalation and Maintenance Phases to continue to take the same dose of lamotrigine, without interruption, during the Continuation Phase. This process also allowed subjects who received blinded placebo during the Escalation and Maintenance Phases to be escalated onto open-label lamotrigine appropriately during the Continuation Phase. An unblinded central pharmacist managed the combination of open-label lamotrigine and blinded study drugs.

Subjects who discontinued prematurely from the study treatment
Subjects who discontinued prematurely from the study treatment due to exacerbation of seizure activity or intolerable, but not medically serious, side effects were offered the option to participate in the open-label Continuation Phase for a long-term follow up and receive open-label lamotrigine, if clinically appropriate, for up to 1 year (52 weeks). These subjects followed the same procedures outlined for subjects who completed the Maintenance Phase.

Primary efficacy endpoint
The primary efficacy endpoint was percent change from Baseline in average monthly PGTC seizure frequency.
Subjects recorded the number of seizures, by seizure type, as well as duration of episodes of innumerable seizure activity in their daily diaries during all phases of this study. If the subjects experienced myoclonic seizures, the number of days on which myoclonus occurred was recorded. The site personnel transcribed the diary information into the CRF, with the diary pages serving as source documentation.

Pharmacokinetic Assessments

Trough lamotrigine serum levels were assessed at Screen and Treatment Weeks 7, 11, and 24 (subjects 2-12 years of age) or Screen and Treatment Weeks 7, 11, and 19 (subjects aged >12 years of age).
These serum levels were measured by radioimmunoassay at GSK, RTP, North Carolina at the initiation of the study until questions were raised in a different study using the same assay. The sample analysis was then outsourced to Advion Biosciences and the assay methodology changed to LC/MS/MS.

Lamotrigine and the internal standard, [$^{13}C2^{15}N5$] lamotrigine, were extracted from human serum by solid phase extraction. Extracts were analysed by HPLC-MS/MS analysis using a Turbo Ion Spray interface and multiple reaction monitoring in the positive ion mode. The method had a lower limit of quantification (LLQ) of 4 ng/mL for lamotrigine using a 50 uL aliquot of human serum. Linearity was demonstrated up to the higher limit of quantification (HLQ) of 4,000ng/mL for lamotrigine.
Each batch of experimental samples was run against duplicate calibration standards, along with the stored Quality Control (QC) samples. Performance of the method, as assessed from determination of lamotrigine in the QC samples, showed that average precision/bias was within (b) (4).

ASSAY VALIDATION

Analyte Validation Range
Lamotrigine 4 to 4000 ng/mL
Dates Samples Received at Advion:
Study dates: Feb 6, 2001-Mar 24, 2004
Assay Period:
9 December 2002-16 July 2004

Possible storage time of 36 months (Feb. 2001-December 2002) -665 days

Assay Validation

Parameter	Lamotrigine
Method	Turbo ion spray liquid chromatography/tandem mass spectrometry (LC/MS/MS)
Freeze-thaw	3 cycles
Benchtop Stability at RT	3 days
Long term at –20° C	975 days

Recovery Low Med High	(b) (4)

Plasma Analysis Results

Parameter	
Method	Turbo ion spray liquid chromatography/tandem mass spectrometry (LC/MS/MS)
Sensitivity/LOQ	4 ng/ml
Linearity (Standard curve samples)	4-4000 ng/ml
Quality Control (QC) Samples	12, 1600, 3200, 1200 ng/ml
Precision of Standards (%CV)	12%@ 4 ng/ml 1.3%@ 4000 ng/ml
Precision of QC Samples (%CV)	12%@ 12 ng/ml 7.8%@ 1200 ng/ml
Accuracy of Standards (%)	99.2%@ 0.25 ng/ml 93%@ 10.2 ng/ml
Accuracy of QC Samples (%)	4%@ 12 ng/ml 1%@ 1200 ng/ml

Pharmacokinetic Measures

Trough lamotrigine serum levels were summarized by mean, median, standard deviation, minimum and maximum.

RESULTS

A total of 117 subjects were randomized and received at least one dose of study drug. Fifty-eight subjects were randomized to the lamotrigine treatment group and 59 subjects were randomized to the placebo treatment group. A greater percentage of subjects in the

placebo treatment group (7%) compared with the lamotrigine treatment group (0 subjects) were prematurely discontinued due lack of efficacy; a greater percentage of subjects in the lamotrigine treatment group (9%) compared with the placebo treatment group (3%) were prematurely discontinued due an AE; likewise, a greater percentage of subjects in the lamotrigine treatment group (9%) compared with the placebo treatment group (2%) were prematurely discontinued due to "lost to follow-up."

Table 4. Demographic Characteristics (ITT Population: Study LAM40097)

Demographic Characteristic	LTG N=58	PBO N=59
Gender, n (%)		
Male	29 (50)	33 (56)
Female	29 (50)	26 (44)
Age (yr)		
Mean (SD)	26.9 (14.6)	24.9 (13.8)
Range	2-53	2-55
Race, n (%)		
White	33 (57)	28 (47)
Black	9 (16)	10 (17)
Hispanic	16 (28)	21 (36)
Age Stratum, n (%)		
2-12 years	12 (21)	11 (19)
>12 years	46 (79)	48 (81)

Table 5. Concurrent AED Therapy (ITT Population: Study LAM40097)

Concurrent AED Therapy	LTG N=58 n (%)	PBO N=59 n (%)
VPA (with or without another AED)	25 (43)	28 (47)
EIAED (without VPA)	27 (47)	24 (41)
Other (no VPA and no EIAED)	6 (10)	7 (12)

Concurrent Medications

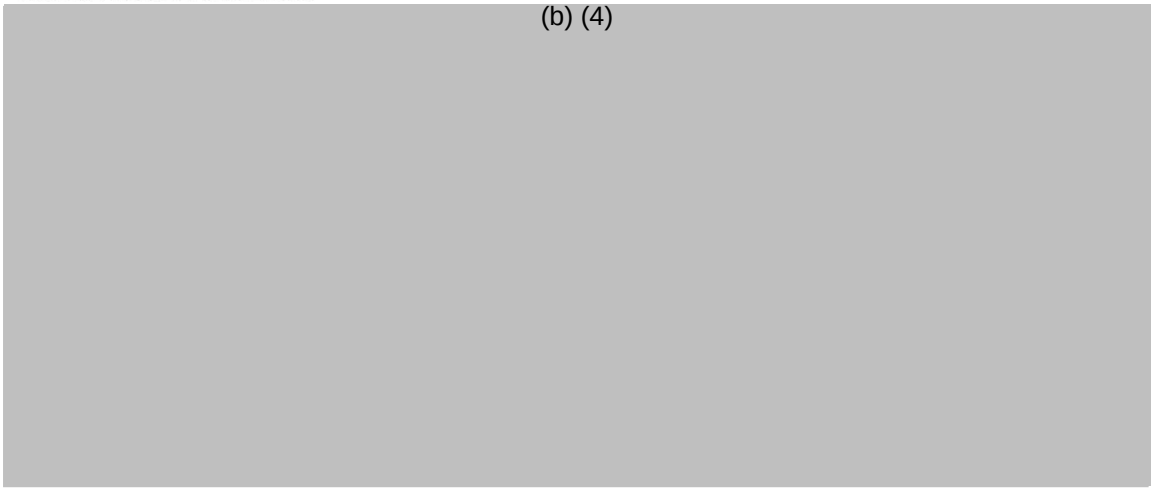
A total of 44 subjects (76%) in the lamotrigine treatment group and 46 subjects (78%) in the placebo treatment group took one or more concurrent medications.

Every subject took a concurrent AED medication. The frequency of concurrent AED medications was similar between the two treatment groups. Half of the subjects in the lamotrigine treatment group took one AED; half took two AEDs. In the placebo treatment group, 59% of subjects took one AED; 41% took two AEDs.

Tables with mean lamictal trough data are presented in the Appendix for the different subgroups in the study.

PROPOSED LABEL

(b) (4)



6 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

___X___ Draft Labeling (b4)

___X___ Draft Labeling (b5)

_____ Deliberative Process (b5)

_____ Law Enforcement Action (b7)

CURRENT IN USE LABEL-PDR- LABEL

Drug Interactions: The net effects of drug interactions with LAMICTAL are summarized in Table 3 (see also DOSAGE AND ADMINISTRATION).

Bupropion: The pharmacokinetics of a 100-mg single dose of LAMICTAL in healthy volunteers (n = 12) were not changed by co-administration of bupropion sustained-release formulation (150 mg twice a day) starting 11 days before LAMICTAL.

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

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

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

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

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

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

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

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

Gradual transient increases in lamotrigine levels will occur during the week of no active hormone preparation (pill-free week) for women not also taking a drug that increases the clearance of lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). The increase in lamotrigine levels will be greater if the dose of LAMICTAL is increased in the few days before or during the pill-free week.

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

The effects of doses of LAMICTAL other than 300 mg/day have not been studied in clinical trials.

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

Dosage adjustments may be necessary for women receiving oral contraceptive preparations (see DOSAGE AND ADMINISTRATION: Women and Oral Contraceptives).

Other Hormonal Contraceptives or Hormone Replacement Therapy: The effect of other hormonal contraceptive preparations or hormone replacement therapy on the pharmacokinetics of lamotrigine has not been evaluated, although the effect may be similar to oral contraceptive preparations. Therefore, as for oral contraceptives, dosage adjustments may be necessary (see DOSAGE AND ADMINISTRATION: Women and Oral Contraceptives).

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

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

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

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

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

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

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

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

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

Table 3. Summary of Drug Interactions With LAMICTAL

Drug	Drug Plasma Concentration With Adjunctive LAMICTAL*	Lamotrigine Plasma Concentration With Adjunctive Drugs†
Bupropion	Not assessed	↔
Carbamazepine (CBZ)	↔	↓

CBZ epoxide[‡]	?	
Ethinylestradiol/levonorgestrel[§]	↔[‖]	↓
Levetiracetam	↔	↔
Lithium	↔	Not assessed
Olanzapine	↔	↔[¶]
Oxcarbazepine	↔	↔
10-monohydroxy oxcarbazepine metabolite[#]	↔	
Phenobarbital/primidone	↔	↓
Phenytoin (PHT)	↔	↓
Rifampin	Not assessed	↓
Valproate	↓	↑
Valproate + PHT and/or CBZ	Not assessed	↔

* From adjunctive clinical trials and volunteer studies.

† Net effects were estimated by comparing the mean clearance values obtained in adjunctive clinical trials and volunteers studies.

‡ Not administered, but an active metabolite of carbamazepine.

↔ = No significant effect.

? = Conflicting data.

§ The effect of other hormonal contraceptive preparations or hormone replacement therapy on the pharmacokinetics of lamotrigine has not been evaluated, although the effect may be similar.

‖ Modest decrease in levonorgestrel (see PRECAUTIONS: Drug Interactions: Effect of LAMICTAL on Oral Contraceptives).

¶ Slight decrease, not expected to be clinically relevant

Not administered, but an active metabolite of oxcarbazepine.

COMMENTS

1.2-12 yrs had slightly higher mean (11%) trough plasma concentrations ng/ml at wk 19 than those >12 (ie 5081 vs 4558).

2. Females had a higher (30%) mean trough plasma concentration ng/ml at wk 19 or 24 than males (ie 5297 vs 4102).

3. Blacks had higher mean trough plasma concentrations ng/ml at wk 19 or 24 than Whites or Hispanics(ie 6564 vs 4656 and 3664). Blacks trough plasma concentrations ng/ml at wk 19 or 24 were 79% higher than Hispanics and 41% higher than Whites.

4. There was no relationship between age and lamotrigine mean trough serum levels ng/ml for subjects taking valproic acid (6983-2 to 12 and 6963 >12 yrs of age).

5. The mean lamotrigine trough serum levels ng/ml for subjects on other EIAED regimens were similar at wk 19 or 24 for younger subjects (3052-2 to12 yr and 2908 >12 yrs of age).

6. There was no relationship between age and lamotrigine mean trough serum levels ng/ml for subjects taking "other AEDs" (3557-2 to12 yr and 3321 >12 yrs of age).

7. There was no relationship between age and lamotrigine mean trough serum levels ng/ml for subjects taking " VPA alone" (5984-2 to12 and 6448 >12 yrs of age).

8. Younger subjects 2-12 taking VPA plus non-inducers had higher lamotrigine mean trough serum levels 9980 ng/ml than did older subjects >12 yrs ,8008 ng/ml. The levels were 25% higher.

9.The only statistically significant findings were related to ethnic origin black vs white (hispanics were not included in the study population) for subjects on Divalproex that received adjunct Lamictal. There was a significant statistical difference between blacks and whites for the total maintenance dose in these subjects 16292 mg vs 7086 mg at the end of the 12 week study. The analysis is presented in the Appendix II.

10. The labeling changes proposed by the firm are in agreement with the current in-use label which is being listed and is the FDA version of the label in the PDR. The firm has supplied data to support the new information in the label.

SIGNATURES

Andre Jackson_____

RD/FT Initialed by Ray Baweja, Ph.D._____
Team Leader

Cc-IND 21-241, HFD-860(Jackson, Baweja, Rahman, Mehta), Central Documents Room(Biopharm-CDR)

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APPENDIX I

Concurrent AED Dosing

A summary of the dosing for the most common concurrent AEDs (valproate, phenytoin, topiramate, and carbamazepine) is summarized in Table A1. The dosing of the most common concurrent AEDs was similar between the two treatment groups.

Summary of Concurrent AED Use

Medication	Lamictal (N=58)	Placebo (N=59)
Any AED Medication	58 (100%)	59 (100%)
Divalproex Sodium	16 (28%)	16 (27%)
Phenytoin	18 (31%)	13 (22%)
Sodium valproate	8 (14%)	12 (20%)
Topiramate	12 (21%)	7 (12%)
Carbamazepine	7 (12%)	10 (17%)
Phenobarbital	5 (9%)	6 (10%)
Clonazepam	3 (5%)	6 (10%)
Levetiracetam	3 (5%)	4 (7%)
Clobazam	3 (5%)	2 (3%)
Oxcarbazepine	3 (5%)	2 (3%)
Zonisamide	3 (5%)	1 (2%)
Gabapentin	1 (2%)	1 (2%)
Other	1 (2%)	1 (2%)
Pentobarbital	1 (2%)	1 (2%)
Ethosuximide	0	1 (2%)
Felbamate	1 (2%)	0

Other AED's such as Tiagabine, Primidone, Vigabatin and Pregabalin were not studied because they are usually not prescribed as adjunct therapy for GTCS.-

PHARMACOKINETIC RESULTS

Lamotrigine Serum Concentrations

The median trough serum concentrations at Visit 8/9 were 3.7mcg/mL for the lamotrigine treatment group Table A2.

Summary of Lamotrigine Trough Serum Concentrations (ng/mL)

Treatment	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Lamictal	Vis 1/Scrn	34	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	40	3496.9	2612.0	2703.0	217.9	13768.3
	Vis 6/Wk 11	39	5327.7	3414.9	4448.7	809.6	14513.9
	Vis8or9/Wk19or24	38	4668.3	3210.0	3659.7	83.2	13592.9
	Early WD	7	4111.5	4113.8	2289.1	970.6	12361.1
Placebo	Vis 1/Scrn	33	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	40	0.0	0.0	0.0	0.0	0.0
	Vis 6/Wk 11	31	0.2	0.9	0.0	0.0	5.1
	Vis8or9/Wk19or24	27	181.3	877.9	0.0	0.0	4566.7
	Early WD	5	892.2	1995.1	0.0	0.0	4461.1

Subgroup Analyses for Lamotrigine Serum Concentrations

Subgroup analyses for lamotrigine trough serum concentrations are provided in the following tables:

1. AGE

Summary of Lamotrigine Trough Serum Concentrations (ng/mL): Subjects 2-12 years of age

Treatment	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Lamictal	Vis 1/Scrn	8	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	11	2101.7	1362.6	2021.3	217.9	4755.9
	Vis 6/Wk 11	9	5081.5	3074.6	4448.7	809.6	11308.6
	Vis8or9/Wk19or24	8	5081.2	2679.9	3855.5	2450.5	9980.8
	Early WD	2	2570.6	398.2	2570.6	2289.1	2852.2
Placebo	Vis 1/Scrn	7	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	9	0.0	0.0	0.0	0.0	0.0
	Vis 6/Wk 11	8	0.6	1.8	0.0	0.0	5.1
	Vis8or9/Wk19or24	7	9.7	25.7	0.0	0.0	68.0
	Early WD	1	0.0		0.0	0.0	0.0

Summary of Lamotrigine Trough Serum Concentrations (ng/mL): Subjects > 12 years of age

Treatment	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Lamictal	Vis 1/Scrn	26	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	29	4026.1	2790.1	3386.4	817.6	13768.3
	Vis 6/Wk 11	30	5401.5	3556.5	4666.7	1360.9	14513.9
	Vis8or9/Wk19or24	30	4558.2	3369.4	3530.9	83.2	13592.9
	Early WD	5	4727.8	4866.5	2196.2	970.6	12361.1
Placebo	Vis 1/Scrn	26	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	31	0.0	0.0	0.0	0.0	0.0
	Vis 6/Wk 11	23	0.0	0.0	0.0	0.0	0.0
	Vis8or9/Wk19or24	20	241.4	1019.7	0.0	0.0	4566.7
	Early WD	4	1115.3	2230.6	0.0	0.0	4461.1

2.GENDER

Summary of Lamotrigine Trough Serum Concentrations (ng/mL): Female Subjects

Treatment	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Lamictal	Vis 1/Scrn	19	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	23	3924.1	3016.8	2817.8	789.5	13768.3
	Vis 6/Wk 11	20	5787.3	3807.3	4892.5	1360.9	14513.9
	Vis8or9/Wk19or24	18	5297.3	3765.4	3892.8	1157.9	13592.9
	Early WD	6	3663.8	4315.6	2242.7	970.6	12361.1
Placebo	Vis 1/Scrn	15	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	15	0.0	0.0	0.0	0.0	0.0
	Vis 6/Wk 11	11	0.5	1.5	0.0	0.0	5.1
	Vis8or9/Wk19or24	8	570.8	1614.6	0.0	0.0	4566.7
	Early WD	1	0.0		0.0	0.0	0.0

Summary of Lamotrigine Trough Serum Concentrations (ng/mL): Male Subjects

Treatment	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Lamictal	Vis 1/Scrn	15	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	17	2919.0	1870.4	2476.2	217.9	8272.6
	Vis 6/Wk 11	19	4843.8	2972.6	4448.7	809.6	12354.0
	Vis8or9/Wk19or24	20	4102.2	2582.1	3555.6	83.2	9980.8
	Early WD	1	6797.5		6797.5	6797.5	6797.5
Placebo	Vis 1/Scrn	18	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	25	0.0	0.0	0.0	0.0	0.0
	Vis 6/Wk 11	20	0.0	0.0	0.0	0.0	0.0
	Vis8or9/Wk19or24	19	17.3	61.0	0.0	0.0	260.9
	Early WD	4	1115.3	2230.6	0.0	0.0	4461.1

ETHNIC ORIGIN

Summary of Lamotrigine Trough Serum Concentrations (ng/mL): White Subjects

Treatment	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Lamictal	Vis 1/Scrn	16	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	20	3869.9	2860.5	3500.1	789.5	13768.3
	Vis 6/Wk 11	17	5771.2	3918.3	5436.1	1422.8	14513.9
	Vis8or9/Wk19or24	18	4656.3	3495.1	3673.6	1157.9	13592.9
	Early WD	6	4415.2	4419.6	2524.2	970.6	12361.1
Placebo	Vis 1/Scrn	14	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	17	0.0	0.0	0.0	0.0	0.0
	Vis 6/Wk 11	10	0.0	0.0	0.0	0.0	0.0
	Vis8or9/Wk19or24	12	380.6	1318.3	0.0	0.0	4566.7
	Early WD	2	0.0	0.0	0.0	0.0	0.0

Summary of Lamotrigine Trough Serum Concentrations (ng/mL): Black Subjects

Treatment	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Lamictal	Vis 1/Scrn	6	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	7	4750.6	3287.4	5978.8	217.9	8310.5
	Vis 6/Wk 11	8	6436.2	4186.8	7467.3	809.6	12354.0
	Vis8or9/Wk19or24	7	6564.2	3113.9	6802.4	1449.6	10860.9
	Early WD	0					
Placebo	Vis 1/Scrn	5	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	7	0.0	0.0	0.0	0.0	0.0
	Vis 6/Wk 11	6	0.0	0.0	0.0	0.0	0.0
	Vis8or9/Wk19or24	3	0.0	0.0	0.0	0.0	0.0
	Early WD	3	1487.0	2575.6	0.0	0.0	4461.1

Summary of Lamotrigine Trough Serum Concentrations (ng/mL): Hispanic Subjects

Treatment	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Lamictal	Vis 1/Scrn	12	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	13	2248.1	987.6	2309.1	1021.0	4047.1
	Vis 6/Wk 11	14	4155.7	1805.8	3662.1	1360.9	7206.5
	Vis8or9/Wk19or24	13	3664.0	2535.2	3435.7	83.2	9980.8
	Early WD	1	2289.1		2289.1	2289.1	2289.1
Placebo	Vis 1/Scrn	14	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	16	0.0	0.0	0.0	0.0	0.0
	Vis 6/Wk 11	15	0.3	1.3	0.0	0.0	5.1
	Vis8or9/Wk19or24	12	27.4	76.1	0.0	0.0	260.9
	Early WD	0					

EFFECT OF VPA REGIMEN

Summary of Lamotrigine Trough Serum Concentrations (ng/mL): Subjects taking VPA regime

Treatment	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Lamictal	Vis 1/Scrn	16	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	19	4694.2	3097.2	3996.8	217.9	13768.3
	Vis 6/Wk 11	16	6492.6	3629.4	6853.4	809.6	14513.9
	Vis8or9/Wk19or24	16	6968.9	3372.3	6708.6	1714.1	13592.9
	Early WD	5	5122.7	4552.3	2852.2	1313.7	12361.1
Placebo	Vis 1/Scrn	13	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	19	0.0	0.0	0.0	0.0	0.0
	Vis 6/Wk 11	13	0.0	0.0	0.0	0.0	0.0
	Vis8or9/Wk19or24	14	344.8	1217.1	0.0	0.0	4566.7
	Early WD	2	2230.6	3154.5	2230.6	0.0	4461.1

Summary of Lamotrigine Trough Serum Concentrations (ng/mL):
Subjects 2-12 years of age taking VPA regimen

Treatment	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Lamictal	Vis 1/Scrn	5	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	7	2376.3	1612.3	2425.5	217.9	4755.9
	Vis 6/Wk 11	6	5621.7	3597.1	5538.2	809.6	11308.6
	Vis8or9/Wk19or24	4	6983.6	2574.1	7095.9	3762.0	9980.8
	Early WD	2	2570.6	398.2	2570.6	2289.1	2852.2
Placebo	Vis 1/Scrn	3	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	5	0.0	0.0	0.0	0.0	0.0
	Vis 6/Wk 11	4	0.0	0.0	0.0	0.0	0.0
	Vis8or9/Wk19or24	4	0.0	0.0	0.0	0.0	0.0
	Early WD	0					

Summary of Lamotrigine Trough Serum Concentrations (ng/mL):
Subjects > 12 years of age taking VPA regimen

Treatment	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Lamictal	Vis 1/Scrn	11	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	12	6046.3	2977.6	5453.6	3386.4	13768.3
	Vis 6/Wk 11	10	7015.2	3735.9	7191.1	1671.4	14513.9
	Vis8or9/Wk19or24	12	6963.9	3701.5	6708.6	1714.1	13592.9
	Early WD	3	6824.1	5523.7	6797.5	1313.7	12361.1
Placebo	Vis 1/Scrn	10	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	14	0.0	0.0	0.0	0.0	0.0
	Vis 6/Wk 11	9	0.0	0.0	0.0	0.0	0.0
	Vis8or9/Wk19or24	10	482.8	1437.3	0.0	0.0	4566.7
	Early WD	2	2230.6	3154.5	2230.6	0.0	4461.1

EFFECT OF EIAED REGIMEN

Summary of Lamotrigine Trough Serum Concentrations (ng/mL):
Subjects taking EIAED regimen

Treatment	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Lamictal	Vis 1/Scrn	13	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	18	2409.9	1490.1	2086.2	817.6	6857.4
	Vis 6/Wk 11	21	4597.0	3138.5	3646.6	1360.9	12551.3
	Vis8or9/Wk19or24	19	2931.2	1875.8	2647.1	83.2	8449.0
	Early WD	1	2196.2		2196.2	2196.2	2196.2
Placebo	Vis 1/Scrn	15	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	16	0.0	0.0	0.0	0.0	0.0
	Vis 6/Wk 11	13	0.4	1.4	0.0	0.0	5.1
	Vis8or9/Wk19or24	10	6.8	21.5	0.0	0.0	68.0
	Early WD	3	0.0	0.0	0.0	0.0	0.0

Summary of Lamotrigine Trough Serum Concentrations (ng/mL):
Subjects 2-12 years of age taking EIAED regimen

Treatment	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Lamictal	Vis 1/Scrn	2	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	3	1705.5	847.0	1442.6	1021.0	2652.7
	Vis 6/Wk 11	3	4000.9	1684.7	3574.2	2570.7	5857.9
	Vis8or9/Wk19or24	3	3052.6	791.3	2758.4	2450.5	3948.9
Placebo	Vis 1/Scrn	2	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	2	0.0	0.0	0.0	0.0	0.0
	Vis 6/Wk 11	2	2.5	3.6	2.5	0.0	5.1
	Vis8or9/Wk19or24	1	68.0		68.0	68.0	68.0
	Early WD	1	0.0		0.0	0.0	0.0

Summary of Lamotrigine Trough Serum Concentrations (ng/mL):
Subjects > 12 years of age taking EIAED regimen

Treatment	Planned Relative Time	n	Mean	SD	Median	Min.
Lamictal	Vis 1/Scrn	11	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	15	2550.8	1570.4	2129.0	817.6
	Vis 6/Wk 11	18	4696.3	3343.9	3698.3	1360.9
	Vis8or9/Wk19or24	16	2908.5	2033.5	2548.6	83.2
	Early WD	1	2196.2		2196.2	2196.2
Placebo	Vis 1/Scrn	13	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	14	0.0	0.0	0.0	0.0
	Vis 6/Wk 11	11	0.0	0.0	0.0	0.0
	Vis8or9/Wk19or24	9	0.0	0.0	0.0	0.0
	Early WD	2	0.0	0.0	0.0	0.0

6.OTHER AEDS

Summary of Lamotrigine Trough Serum Concentrations (ng/mL):
Subjects taking other AED regimen

Treatment	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Lamictal	Vis 1/Scrn	5	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	3	2436.7	1374.1	1954.3	1368.8	3987.0
	Vis 6/Wk 11	2	3680.6	3193.0	3680.6	1422.8	5938.4
	Vis8or9/Wk19or24	3	3399.8	491.6	3557.3	2848.8	3793.4
	Early WD	1	970.6		970.6	970.6	970.6
Placebo	Vis 1/Scrn	5	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	5	0.0	0.0	0.0	0.0	0.0
	Vis 6/Wk 11	5	0.0	0.0	0.0	0.0	0.0
	Vis8or9/Wk19or24	3	0.0	0.0	0.0	0.0	0.0
	Early WD	0					

Summary of Lamotrigine Trough Serum Concentrations (ng/mL):
Subjects 2-12 years of age taking other AED regimen

Treatment	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Lamictal	Vis 1/Scrn	1	(b) (4)				
	Vis 5/Wk 7	1					
	Vis 6/Wk 11	0					
	Vis8or9/Wk19or24	1					
Placebo	Vis 1/Scrn	2	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	2	0.0	0.0	0.0	0.0	0.0
	Vis 6/Wk 11	2	0.0	0.0	0.0	0.0	0.0
	Vis8or9/Wk19or24	2	0.0	0.0	0.0	0.0	0.0

Summary of Lamotrigine Trough Serum Concentrations (ng/mL):
Subjects > 12 years of age taking other AED regimen

Treatment	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Lamictal	Vis 1/Scrn	4	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	2	2970.6	1437.3	2970.6	1954.3	3987.0
	Vis 6/Wk 11	2	3680.6	3193.0	3680.6	1422.8	5938.4
	Vis8or9/Wk19or24	2	3321.1	668.0	3321.1	2848.8	3793.4
	Early WD	1	970.6		970.6	970.6	970.6
Placebo	Vis 1/Scrn	3	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	3	0.0	0.0	0.0	0.0	0.0
	Vis 6/Wk 11	3	0.0	0.0	0.0	0.0	0.0
	Vis8or9/Wk19or24	1	0.0		0.0	0.0	0.0
	Early WD	0					

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7.EFFECT OF AGE ON REGIMEN OF VPA ALONE

Summary of Lamotrigine Trough Serum Concentrations (ng/mL):
Subjects taking VPA alone

Treatment	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Lamictal	Vis 1/Scrn	7	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	10	3661.4	2446.5	3612.0	217.9	8272.6
	Vis 6/Wk 11	7	7064.0	3515.2	7206.5	809.6	11308.6
	Vis8or9/Wk19or24	7	6249.7	2582.5	6600.8	3435.7	10860.9
	Early WD	3	5509.0	5983.7	2852.2	1313.7	12361.1
Placebo	Vis 1/Scrn	8	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	10	0.0	0.0	0.0	0.0	0.0
	Vis 6/Wk 11	8	0.0	0.0	0.0	0.0	0.0
	Vis8or9/Wk19or24	8	32.6	92.3	0.0	0.0	260.9
	Early WD	2	2230.6	3154.5	2230.6	0.0	4461.1

Summary of Lamotrigine Trough Serum Concentrations (ng/mL):
Subjects 2-12 years of age taking VPA alone

Treatment	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Lamictal	Vis 1/Scrn	3	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	5	2042.0	1761.3	2021.3	217.9	4755.9
	Vis 6/Wk 11	4	5911.5	4422.0	5764.0	809.6	11308.6
	Vis8or9/Wk19or24	3	5984.6	1987.5	6600.8	3762.0	7591.0
	Early WD	1	2852.2		2852.2	2852.2	2852.2
Placebo	Vis 1/Scrn	1	0.0		0.0	0.0	0.0
	Vis 5/Wk 7	2	0.0	0.0	0.0	0.0	0.0
	Vis 6/Wk 11	2	0.0	0.0	0.0	0.0	0.0
	Vis8or9/Wk19or24	2	0.0	0.0	0.0	0.0	0.0
	Early WD	0					

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Summary of Lamotrigine Trough Serum Concentrations (ng/mL):
Subjects > 12 years of age taking VPA alone

Treatment	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Lamictal	Vis 1/Scrn	4	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	5	5280.7	1951.5	4928.4	3386.4	8272.6
	Vis 6/Wk 11	3	8600.5	1241.6	9007.6	7206.5	9587.5
	Vis8or9/Wk19or24	4	6448.5	3253.0	5748.7	3435.7	10860.9
	Early WD	2	6837.4	7811.7	6837.4	1313.7	12361.1
Placebo	Vis 1/Scrn	7	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	8	0.0	0.0	0.0	0.0	0.0
	Vis 6/Wk 11	6	0.0	0.0	0.0	0.0	0.0
	Vis8or9/Wk19or24	6	43.5	106.5	0.0	0.0	260.9
	Early WD	2	2230.6	3154.5	2230.6	0.0	4461.1

8. EFFECT OF AGE ON SUBJECTS TAKING VPA WITH NON-INDUCERS AND INDUCERS

Summary of Lamotrigine Trough Serum Concentrations (ng/mL):
Subjects taking VPA plus non-Inducers

Treatment	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Lamictal	Vis 1/Scrn	7	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	8	6120.2	3599.6	5076.6	2426.9	13768.3
	Vis 6/Wk 11	8	6595.4	3738.6	6031.8	3429.5	14513.9
	Vis8or9/Wk19or24	8	8255.0	3507.3	7875.2	3508.0	13592.9
	Early WD	1	2289.1		2289.1	2289.1	2289.1
Placebo	Vis 1/Scrn	4	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	7	0.0	0.0	0.0	0.0	0.0
	Vis 6/Wk 11	4	0.0	0.0	0.0	0.0	0.0
	Vis8or9/Wk19or24	5	913.3	2042.3	0.0	0.0	4566.7

Summary of Lamotrigine Trough Serum Concentrations (ng/mL):
Subjects 2-12 years of age taking VPA plus non-Inducers

Treatment	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Lamictal	Vis 1/Scrn	2	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	2	3211.8	1110.1	3211.8	2426.9	3996.8
	Vis 6/Wk 11	2	5042.1	2242.1	5042.1	3456.7	6627.6
	Vis8or9/Wk19or24	1			(b) (4)		
	Early WD	1					
Placebo	Vis 1/Scrn	1	0.0		0.0	0.0	0.0
	Vis 5/Wk 7	2	0.0	0.0	0.0	0.0	0.0
	Vis 6/Wk 11	1	0.0		0.0	0.0	0.0
	Vis8or9/Wk19or24	2	0.0	0.0	0.0	0.0	0.0

Summary of Lamotrigine Trough Serum Concentrations (ng/mL):
Subjects > 12 years of age taking VPA plus non-Inducers

Treatment	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Lamictal	Vis 1/Scrn	5	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	6	7089.6	3658.2	6251.2	3909.5	13768.3
	Vis 6/Wk 11	6	7113.1	4156.4	6305.9	3429.5	14513.9
	Vis8or9/Wk19or24	7	8008.4	3712.6	7739.3	3508.0	13592.9
Placebo	Vis 1/Scrn	3	0.0	0.0	0.0	0.0	0.0
	Vis 5/Wk 7	5	0.0	0.0	0.0	0.0	0.0
	Vis 6/Wk 11	3	0.0	0.0	0.0	0.0	0.0
	Vis8or9/Wk19or24	3	1522.2	2636.6	0.0	0.0	4566.7

Summary of Lamotrigine Trough Serum Concentrations (ng/mL):
Subjects ≥ 12 years of age taking VPA plus Inducers

Treatment	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
Lamictal	Vis 1/Scrn	1	(b) (4)				
	Vis 5/Wk 7	0					
	Vis 6/Wk 11	1					
	Vis8or9/Wk19or24	1					
	Early WD	0					
Placebo	Vis 1/Scrn	0					
	Vis 5/Wk 7	1	0.0		0.0	0.0	0.0
	Vis 6/Wk 11	0					
	Vis8or9/Wk19or24	1	0.0		0.0	0.0	0.0

2 Page(s) Withheld

___X___ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

_____ Law Enforcement Action (b7)

APPENDIX III-OXCARBAZEPINE

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG:LAMOTRIGINE **PRIMARY REVIEWER**: Andre Jackson
NDA:20241 **TYPE: Labeling Supplement**

FORMULATION:Tablet **STRENGTH: 100 mg/day -400 mg/day**
APPLICANT:Glaxo Smith Kline Submission Date: June 29, 2004

INDICATIONS:Anti-Epileptic
Generic Name: Lamictal

Drug –Drug Interaction Study SCA10910-Lamotrigine and Oxcarbazepine

Study Introduction and Objectives

Lamotrigine (3,5-diamino-6-(2,3,-dichlorophenyl)-1,2,4-triazine) is currently licensed for use in epilepsy, however, clinical studies have demonstrated its effectiveness in the prevention of depressive mood episodes in patients suffering from bipolar disease. As its efficacy in the prevention of manic episodes has not been shown to be as robust as for the prevention of depressive episodes, it is likely that physicians will want to combine lamotrigine with a drug, such as oxcarbazepine, that may have antimanic properties in bipolar disease. Oxcarbazepine is currently licensed for epilepsy, therefore the results of this study are relevant not only to bipolar disorder but to the prescribing of oxcarbazepine and lamotrigine in epilepsy as well.

Therefore, the objectives of this study were to investigate whether there was any effect of lamotrigine upon the pharmacokinetics of oxcarbazepine or any effect of oxcarbazepine upon lamotrigine at steady state. As the major metabolites of lamotrigine are not pharmacologically active, it was sufficient to investigate the effects on the plasma concentrations of the parent lamotrigine only. In the case of oxcarbazepine, the concentrations of the 10-monohydroxy metabolite (MHD) of oxcarbazepine are more relevant than the concentrations of oxcarbazepine because following oral administration, oxcarbazepine is completely absorbed and extensively metabolised to MHD. The half-lives of the parent and MHD are about 2 hours and 9 hours, respectively, and pharmacological activity in vivo following oxcarbazepine dosing is thought to be due to MHD [Lloyd, 1994].

Specific Objectives

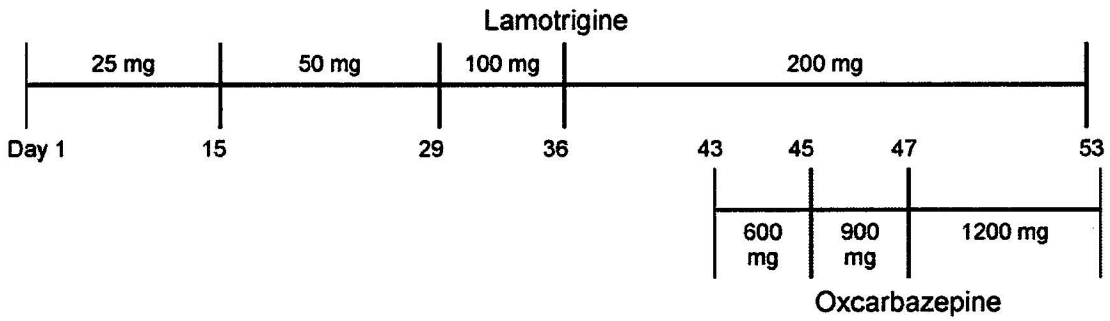
- To investigate whether there was a difference (defined as greater than a 30% change in C_{max} and $AUC_{(0-12)}$) between the plasma pharmacokinetic profile of the 10-monohydroxy metabolite (MHD) of oxcarbazepine when oxcarbazepine was administered alone or when administered with lamotrigine to steady state.
- To investigate whether there was a difference (defined as greater than a 30% change in Cmax and $AUC_{(0-24)}$) between the serum pharmacokinetic profile of lamotrigine when administered alone or when administered with oxcarbazepine to steady state.

Study Design

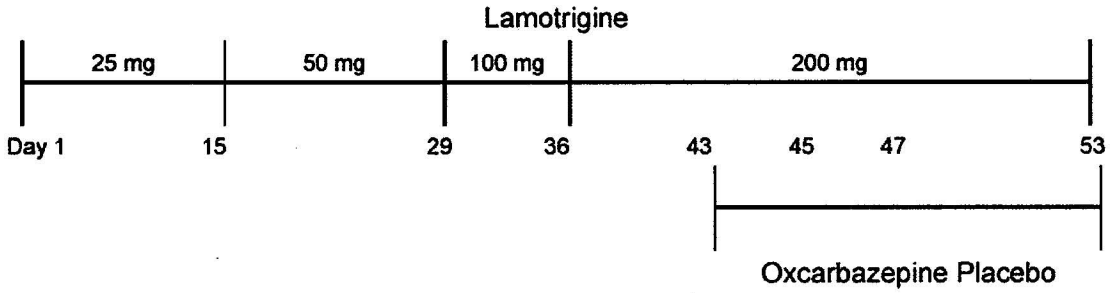
A total of 39 healthy male volunteers aged 18-55 years were originally planned to enter into the study in three parallel cohorts. However due to a high number of withdrawals this was increased to 47. A screening assessment was performed up to 4 weeks prior to dosing. Subjects were randomised into 3 groups to receive (1) lamotrigine/lamotrigine plus oxcarbazepine, (2) lamotrigine/lamotrigine plus oxcarbazepine placebo, and (3) lamotrigine placebo/lamotrigine placebo plus oxcarbazepine. Lamotrigine was titrated from 25 mg to 200 mg per day according to the recommended dose titration schedule. Oxcarbazepine was titrated from 300 mg to 600 mg bd in accordance with the dose titration schedule 5.4.2. On the final dosing day, oxcarbazepine was given as a 600 mg od dose in the morning only. A schematic diagram of the study is shown in Figure 1.

Figure 1 Study Schematic

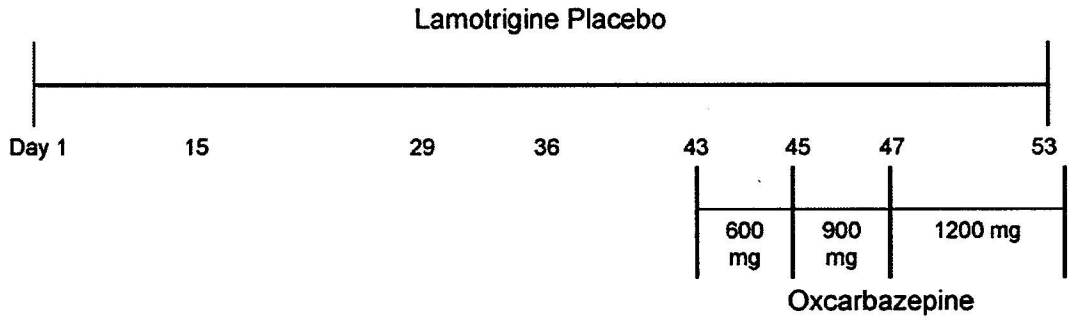
Cohort A



Cohort B



Cohort C



Each cohort comprised an equal number of volunteers who received lamotrigine titrated from 25 mg to 200 mg or lamotrigine placebo (1 or 2 tablets) for 53 days. Between Day 43 and Day 52 oxcarbazepine in titrated doses from 300 mg to 600 mg bd or oxcarbazepine placebo (2 to 4 tablets bd) was added. On Day 53, a final dose of 200 mg lamotrigine and 600 mg (od morning only) was given. By day 53, steady state concentrations had been achieved for both drugs. The pharmacokinetic profile of lamotrigine and oxcarbazepine was obtained on Day 53 over 24 hours and 12 hours respectively.

Lamotrigine

Blood samples for pharmacokinetic analysis of lamotrigine were drawn prior to dosing on Days 51-52 to confirm steady state concentrations of lamotrigine and on the PK profiling day (Day 53) at the following times pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24 hours

MHD and Oxcarbazepine

Blood samples for pharmacokinetic analysis of MHD (the active metabolite of oxcarbazepine) and oxcarbazepine were drawn prior to morning dose on Days 51-52 to confirm steady state concentrations of oxcarbazepine and on the PK profiling day (Day 53) at the following times pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12 hours

Table 1. Demographic and Baseline Characteristics

Demographic Characteristic	Cohort 1 N=15	Cohort 2 N=16	Cohort 3 N=16
Age (Years)			
Mean (SD)	34 (8.9)	31 (8.9)	34 (11.1)
Range	22-53	20-54	19-54
Race, n (%)			
White	15 (100%)	15 (93.8%)	16 (100%)
Black	0 (0%)	1 (6.2%)	0 (0%)
Height (cm)			
Mean (SD)	180 (5.6)	175 (6.9)	179 (7.8)
Range	170-192	159-184	161-189
Weight (kg)			
Mean (SD)	80.9 (7.22)	80.2 (8.77)	83.2 (12.44)
Range	67.5-91.8	62.1-96.1	61.8-103.4
BMI			
Mean (SD)	25.13 (2.32)	26.13 (2.06)	25.99 (3.08)
Range	20.6-28.7	23.1-29.3	21.0-30.5

Data source: Table DS32

Statistical Methods

Log_e-transformed $AUC_{(0-24)}$ and C_{max} of lamotrigine, in the presence and absence of oxcarbazepine, and log_e-transformed $AUC_{(0-12)}$ and C_{max} of MHD, in the presence and absence of lamotrigine, were separately subjected to analysis of variance (ANOVA) by fitting a term for regimen. Data from regimens A and B were used in the model for the effect of oxcarbazepine on lamotrigine and from regimens A and C for the model of the effect of lamotrigine on MHD.

In order to investigate the effects of lamotrigine on MHD pharmacokinetics, point estimates and 90% confidence intervals were constructed for the differences, in the presence and absence of lamotrigine (A-C), in $AUC_{(0-12)}$ and C_{max} of MHD, using the residual variance from the ANOVA. These were backtransformed to obtain the estimates for the ratio "oxcarbazepine + lamotrigine:oxcarbazepine" (A:C).

In order to investigate the effects of oxcarbazepine on lamotrigine pharmacokinetics, point estimates and 90% confidence intervals were constructed for the differences, in the presence and absence of oxcarbazepine (A-B), in $AUC_{(0-24)}$ and C_{max} of lamotrigine, using the residual variance from the ANOVA. These were backtransformed to obtain the estimates for the ratio "oxcarbazepine + lamotrigine:lamotrigine" (A:B).

The pooled between-subject coefficient of variation was calculated for log_e-transformed parameters where:

$$CV_{resid}(\%)=SQRT(exp(MSE) - 1) \times 100$$

where MSE is the residual error from the model.

Distributional assumptions underlying these analyses were assessed by residual plots. Homogeneity of variance was assessed by plotting the studentised residuals against the predicted values from the model, whilst normality was examined by normal plots. If the assumptions were seriously violated then non-parametric methods would have been used to construct 90% confidence intervals, and statistical inference would have been based on these results.

Listings were generated and summary statistics were calculated by regimen for all pharmacokinetic parameters. Geometric means and between-subject coefficients of variation (CV_b) were calculated for log_e-transformed endpoints where:

geometric mean = exp (mean on log scale)

$$CV_b(\%) = SQRT[exp(sd^2 + 1] \times 100$$

where sd is the standard deviation of the log_e-transformed data.

Sample Collection and Handling

Bioanalytical Methods-Lamotrigine

Bioanalytical Methods-Oxcarbazepine

Bioanalytical Procedures-

Studied Period:
Lamotrigine-Assays were conducted from 03-Feb-2003 to 16-Apr 2003.

Oxcarbazepine-
Study Dates-September 30, 2002-April 16, 2003
Assays were conducted from 25-FebJan -2003 to 06-May 2003.
Theoretical storage time: ~240 days
See Appendix for explanation of stability
Assay Validation

Parameter	Lamotrigine	Oxcarbazepine	
Method	LC/MS/MS	HPLC/UV	
Freeze-thaw	3 CYCLES		
Bench top Stability at RT	3 DAYS	4 hrs	
Long term at –20° C	975 DAYS	23 days	
Recovery Low Med High	(b) (4)		

Plasma Analysis Results

Parameter	Lamotrigine	Oxcarbazepine
Method	LC/MS/MS	HPLC/UV
Sensitivity/LOQ	4 ng/ml	0.1 ug/ml
Linearity (Standard curve samples)	4-400 ng/ml	0.1-5 ug/ml
Quality Control (QC) Samples	12, 1600, 3200, 12000 ng/ml	0.3, 1.2, 4.0 ug/ml
Precision of Standards (%CV)	5.8%@ 4 ng/ml 1.8%@ 4000 ng/ml	3% @ 0.1 ug/ml 1.4% @ 5 ug/ml
Precision of QC Samples (%CV)	4.5%@ 12 ng/ml 4%@ 1200 ng/ml	3% @ 0.3 ug/ml 2.7% @ 4 ug/ml
Accuracy of Standards (%)	100%@ 4 ng/ml 97%@ 4000 ng/ml	101% @ 0.1 ug/ml 100.1% @ 5 ug/ml
Accuracy of QC Samples (%)	103%@ 12 ng/ml 101%@ 1200 ng/ml	95% @ 0.3 ug/ml 96% @ 4 ug/ml

Comment:

Statistical Analysis

RESULTS

Effect of oxcarbazepine on Lamotrigine pharmacokinetics

Median serum lamotrigine concentration-time profiles for lamotrigine in the presence and absence of oxcarbazepine are displayed in Figure 2. Following lamotrigine administration with oxcarbazepine or placebo, serum lamotrigine concentrations on day 53 of repeat dosing were quantifiable prior to dosing and concentrations increased following dosing. Peak lamotrigine concentrations were observed between 0.5-4 hours post-dose and declined thereafter, but remained quantifiable for the entire 24-hour post-dose period.

Figure 2 Median serum lamotrigine concentration-time profiles:Regimen A, lamotrigine + oxcarbazepine and Regimen B, lamotrigine + placebo

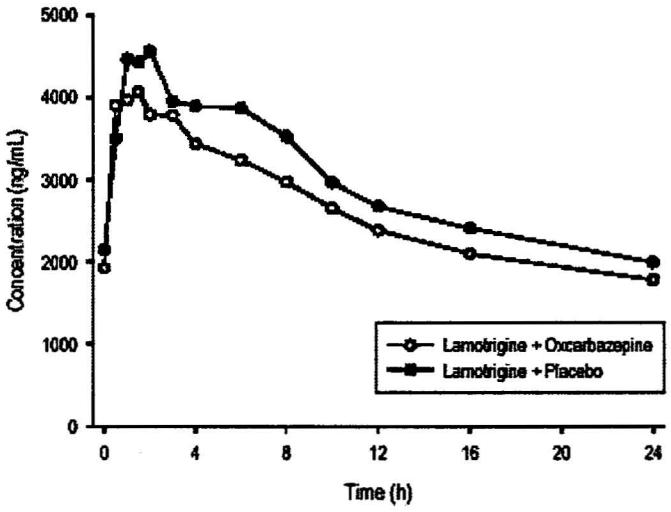


Table 2. Summary geometric mean (range) lamotrigine pharmacokinetic parameters and comparison between regimens

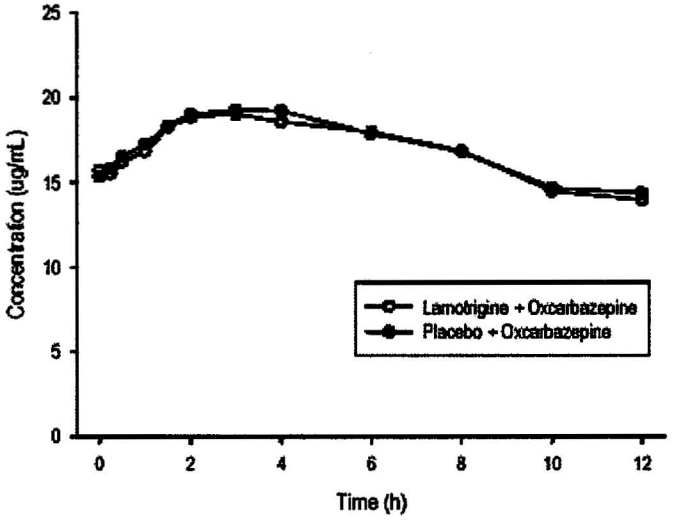
Parameter	Regimen A Lamotrigine + Oxcarbazepine (N=13)	Regimen B Lamotrigine + Placebo (N=13)	Ratio (A:B) of Geometric Means (90% CI)	CVb(%)-A & B Combined)
C_{max} (ng/mL)	4411 (2905-6514)	4479 (3176-5906)	0.98 (0.85, 1.15)	22.8
$AUC_{(0-24)}$ (ng.h/mL)	64202 (44676-98924)	69754 (51697-104027)	0.92 (0.78, 1.08)	24.7
t_{max} (h) [1]	1.00 (0.50-2.00)	1.50 (0.50-4.00)	NA	NA

1. median (range). NA Not applicable.

Effect of Lamotrigine on MHD pharmacokinetics

Median plasma MHD concentration-time profiles when oxcarbazepine was administered in presence and absence of lamotrigine are displayed in Figure 3. Following oxcarbazepine administration with lamotrigine or placebo, plasma MHD concentrations on day 53 of repeat dosing were quantifiable prior to dosing, and concentrations increased following dosing. Peak MHD concentrations were observed between 1-8 hours post-dose and declined thereafter, but remained quantifiable for the entire 24-hour post-dose period.

Figure 3 **Median plasma MHD concentration-time profiles: Regimen A, lamotrigine + oxcarbazepine and Regimen C, oxcarbazepine + placebo**



A summary of pharmacokinetic parameters for MHD of oxcarbazepine is presented in Table 3.

Table 3. Summary geometric mean(range) MHD pharmacokinetic parameters and comparison between regimens Summary

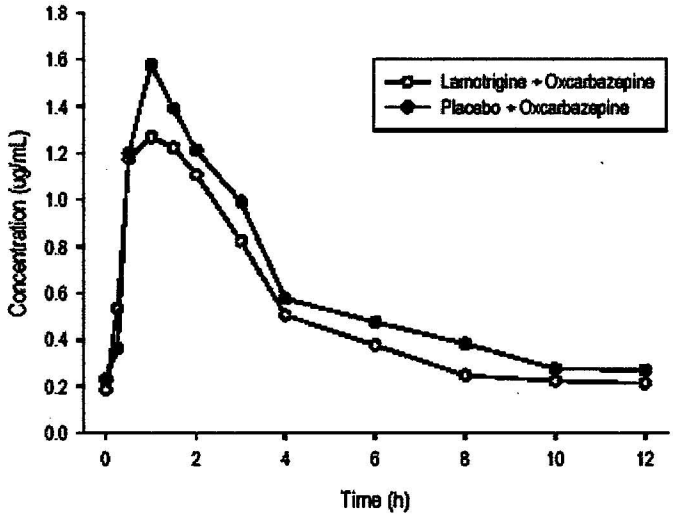
Parameter	Regimen A Lamotrigine + Oxcarbazepine (N=13)	Regimen C Placebo + Oxcarbazepine (N=13)	Ratio (A:C) of Geometric Means (90% CI)	CVb(%)-A & B Combined)
C_{max} (ug/mL)	19.0 (13.8-23.1)	19.7 (15.3-25.1)	0.96 (0.88, 1.06)	14.6
$AUC_{[0-12]}$ (ug.h/mL)	192 (143-239)	204 (158-258)	0.94 (0.86, 1.04)	13.8
t_{max} (h) [1]	3.00 (1.00-4.00)	3.00 (1.50-8.00)	NA	NA

1. median (range). NA Not applicable.
Source: Table 13.2, Table 13.6 and Table 13.7

Effect of Lamotrigine on oxcarbazepine pharmacokinetics

Median plasma oxcarbazepine concentration-time profiles in the presence and absence of lamotrigine are displayed in Figure 4. Following oxcarbazepine administration with lamotrigine or placebo, plasma oxcarbazepine concentrations were quantifiable prior to dosing, and concentrations increased following dosing. Peak oxcarbazepine plasma concentrations were observed between 0.5-3 hours post-dose and declined thereafter, but remained quantifiable for the entire 24-hour post-dose period.

Figure 4 **Median plasma oxcarbazepine concentration-time profiles:Regimen A, lamotrigine + oxcarbazepine and Regimen C, oxcarbazepine + placebo**



A summary of pharmacokinetic parameters for oxcarbazepine is presented in Table

Table . Summary geometric mean(range) of oxcarbazepine pharmacokinetic

Parameter	Regimen A Lamotrigine + Oxcarbazepine (N=13)	Regimen C Placebo + Oxcarbazepine (N=13)
C_{max} (ug/mL)	1.52 (0.726-2.95)	1.66 (0.913-2.74)
$AUC_{(0-12)}$ (ug.h/mL)	6.44 (4.49-9.43)	7.06 (5.00-9.03)
t_{max} (h) [1]	1.00 (0.50-3.00)	1.00 (0.50-3.00)

1. median (range)

Pharmacokinetic conclusions

- Lamotrigine $AUC_{(0-24)}$ and C_{max} at steady state were comparable when lamotrigine was administered alone and when co-administered with oxcarbazepine. $AUC_{(0-24)}$ and C_{max} of lamotrigine were, on average, 8% and 2% lower when lamotrigine was administered with oxcarbazepine, compared to lamotrigine and placebo. The 90% CI's indicated that the true differences lie between 22% lower and 8% higher for $AUC_{(0-24)}$ and between 15% lower and 15% higher for C_{max}.
- MHD $AUC_{(0-12)}$ and C_{max} at steady state were comparable when oxcarbazepine was administered alone and when co-administered with lamotrigine. $AUC_{(0-12)}$ and C_{max} of MHD of oxcarbazepine were, on average, 6% and 4% lower when lamotrigine was administered with oxcarbazepine, compared to oxcarbazepine and placebo. The 90% CI's indicated that the true differences lie between 14% lower and 4% higher for $AUC_{(0-12)}$ and between 12% lower and 6% higher for C_{max}.

SIGNATURES

Andre Jackson_____
Reviewer, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FT Initialed by Ray Baweja, Ph.D._____
Team Leader

Cc-IND 21-241, HFD-860(Jackson, Baweja, Rahman, Mehta), Central Documents Room(Biopharm-CDR)

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APPENDIX

Long term oxcarbazepine plasma stability (SCA10910)

Samples were received at PPD on 08-Jan-04 and 09-Apr-04 and stored initially at -20°C as per the GSK protocol.

1. For the samples received on 08-Jan-04, the samples were stored initially at -20°C. On 12-Feb-04, the 23 day short term stability experiment at -20°C was completed as part of the assay validation and a (b) (4)% negative bias was observed in the stability QC's. Although within the specs of the SOP (allows up to (b) (4)% bias) a decision was made to move the samples into a -80°C freezer as a precaution.
Subsequently, the following stabilities were established :
   a. 36 days of stability at -20°C, covering the time that the samples were stored initially upon receipt.
   b. 214 days of stability at -80°C, more than covering the time from sample receipt to final analysis date.
2. For the samples received on 09-Apr-04, the samples were held for a max of 27 days at -80°C.

APPENDIX IV-RIFAMPICIN

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG:LAMOTRIGINE **PRIMARY REVIEWER**: Andre Jackson
NDA:20241/SLR-025 **TYPE: Labeling Supplement**
20764/SLR-018
FORMULATION:Tablet **STRENGTH: 100 mg/day -400 mg/day**
APPLICANT:Glaxo Smith Kline Submission Date: June 29, 2004

INDICATIONS:Anti-Epileptic
Generic Name: Lamictal

Drug –Drug Interaction Study -Lamotrigine and Rifampicin
Review of Literature Reference

Introduction:

The firm submitted a reference:

U. Ebert, N.Q. Thong, R. Oertel, and W.Kirch, Effects of rifampicin and cimetidine on pharmacokinetics and pharmacodynamics of lamotrigine in healthy subjects. Eur.J. Clin. Pharmacol. 2000 56:299-304.

The authors chose to study rifampicin, a known inducer of the microsomal P450 enzyme system and of specific isoforms of the UDP- glucuronyl-transferase enzyme system and if it could affect the elimination rate of lamotrigine. Therefore, the authors objective was undertaken to assess this potential pharmacokinetic interaction by evaluation of the lamotrigine serum concentration versus time profiles after co-administration with rifampicin.

The study also investigated an interaction with Cimetidine but will not be discussed.

Design

Subjects
In a randomized, placebo-controlled, open labeled, crossover study, ten healthy, non-obese, nonsmoking male subjects (mean age . SD, 25 . 4 years; weight range 63±100 kg, height range 170±189 cm) were investigated. The subjects were randomized using a simple randomization procedure after screening tests were completed.

Study design
The study consisted of three periods (lamotrigine + cimetidine, lamotrigine + rifampicin, and lamotrigine + placebo). All experiments were begun between 0600 hours and 0700

hours. Lamotrigine administration was preceded by a 5-day course of 1) rifampicin (Rifa 600) 600 mg orally at 1900 hours, or (2) placebo (mannit). On the study day (day 6), subjects received single oral doses of 25 mg lamotrigine.

Blood samples of 7.5 ml were collected from an indwelling 18-gauge cannula (Vaso®x BraunuÈ le, B. Braun Melsungen AG, Melsungen, Germany) inserted into the antecubital vein before and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, and 48 h after lamotrigine administration.

Pharmacokinetics of lamotrigine

Figure 1 shows the time profile of lamotrigine serum concentrations (mean ± SEM) after pretreatment with either cimetidine, rifampicin, or placebo. The serum profiles of lamotrigine are similar for placebo and cimetidine pretreatment. In five subjects, a second C_{max} occurred between 2.5 h and 4 h after lamotrigine administration. Pharmacokinetic parameters of lamotrigine are listed in Table 1. Rifampicin significantly

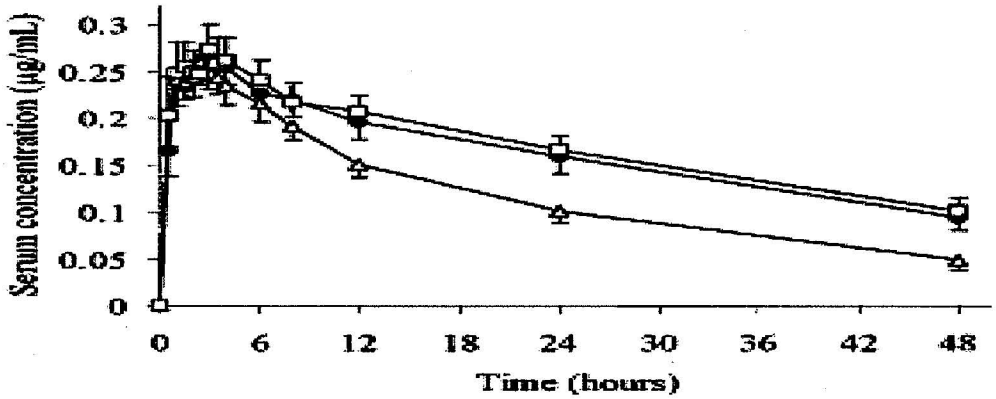

Fig. 1 Serum concentration versus time profile (mean ± SEM) of lamotrigine after administration of a single oral dose of 25 mg after a 5-day pretreatment with placebo (*filled circles*), cimetidine (*open squares*), or rifampicin (*open triangles*)

Table 1 Effect of a 5-day course of cimetidine or rifampicin on pharmacokinetics of lamotrigine determined after administration of a single oral dose of 25 mg lamotrigine (mean ± SEM; $n = 10$). CL/F clearance over bioavailability; CL_R renal clearance; $t_{1/2}$ terminal half-life; MRT mean residence time; $AUC_{0-48\ h}$ area under the lamotrigine serum concentration–time curve; $AUC_{0-\infty}$ total area under the lamotrigine serum concentration–time curve; C_{max} maximum lamotrigine serum concentration; t_{max} time to reach C_{max}

	Lamotrigine + placebo	Lamotrigine + cimetidine	Lamotrigine + rifampicin
CL/F (l/h)	2.60 ± 0.40	2.48 ± 0.35	5.13 ± 1.05*
CL_R (l/h)	0.10 ± 0.03	0.14 ± 0.03	0.16 ± 0.04
$t_{1/2}$ (h)	23.8 ± 2.1	24.2 ± 1.9	14.1 ± 1.7*
MRT (h)	18.4 ± 1.3	19.5 ± 0.4	15.2 ± 1.31*
$AUC_{0-48\ h}$ (µg/ml/min)	477.04 ± 44.83	486.50 ± 50.19	328.30 ± 43.42*
$AUC_{0-\infty}$ (µg/ml/min)	703.99 ± 82.31	718.45 ± 93.40	396.24 ± 60.18*
C_{max} (µg/ml)	0.29 ± 0.02	0.29 ± 0.03	0.29 ± 0.03
t_{max} (h)	1.6 ± 0.28	1.1 ± 0.26	1.1 ± 0.2

*$P < 0.05$ compared with lamotrigine + placebo and lamotrigine + cimetidine using one-way analysis of variance (ANOVA)

Conclusion

After rifampicin, the mean total AUC of lamotrigine reached approximately 56% of the corresponding value in the placebo phase. The effect of rifampicin on lamotrigine pharmacokinetics was consistent in each subject. This was a result of the 97% increase in lamotrigine clearance in the presence of rifampicin.

SIGNATURES

Andre Jackson_____
Reviewer, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FT initialized by Ray Baweja, Ph.D..._____
Team Leader, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

cc: NDA HFD-120, HFD-860(Mehta, Rahman, Baweja, Jackson)

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APPENDIX V-OLANZAPINE

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG:LAMOTRIGINE **PRIMARY REVIEWER**: Andre Jackson
NDA:20241 **TYPE: Labeling Supplement**

FORMULATION:Tablet **STRENGTH: 100 mg/day -400 mg/day**
APPLICANT:Glaxo Smith Kline Submission Date: June 29, 2004

INDICATIONS:Anti-Epileptic
Generic Name: Lamictal

Drug –Drug Interaction Study SCA10908-Lamotrigine and Olanzapine

INTRODUCTION

Lamotrigine (3,5-diamino-6-(2,3,-dichlorophenyl)-1,2,4-triaine) is currently licensed for use in epilepsy however clinical studies have demonstrated it's effectiveness in the prevention of depressive mood episodes in patients suffering from bipolar disease. In the US, the FDA has included prevention of manic episodes as part of the indication. Nonetheless, it is still likely that lamotrigine would be used in combination with clearly antimanic properties

Lamotrigine is not known to inhibit CYP450 enzymes, therefore the likelihood of an inhibition of the metabolism of olanzapine, which is metabolised via multiple p450 and glucuronidation pathways, is low. However, prior to this study, it was unknown whether a possible induction of the glucuronidation pathways by lamotrigine may increase the metabolism of olanzapine. Recent in vitro work suggested that lamotrigine inhibits olanzapine glucuronidation. There were, however, no data showing whether olanzapine may induce or inhibit the glucuronidation of lamotrigine. As both drugs are glucuronidated, the potential for drug interactions involving this pathway exists.

Therefore, the objective of this study was to investigate whether there is any effect of lamotrigine upon the pharmacokinetics of olanzapine or any effect of olanzapine upon lamotrigine at steady state. As the major metabolites of lamotrigine and olanzapine are not pharmacologically active, it was sufficient to investigate any effects on the plasma concentrations of the parent compound.

STUDY OBJECTIVE(S)

Primary

• To investigate whether there is a difference (defined as greater than a 30% change in

C_{max} and $AUC_{(0-24)}$) between the plasma pharmacokinetic profile of olanzapine when administered alone and when administered with lamotrigine to steady state.
• To investigate whether there is a significant difference (defined as greater than a 30% change in C_{max} and $AUC_{(0-24)}$) between the serum pharmacokinetic profile of lamotrigine when administered alone and when administered with olanzapine to steady state.

Secondary

• To investigate the safety and tolerability of lamotrigine after co-administration with olanzapine.

Study Design

Overall Study Design – Description

This was a single centre, randomised, placebo-controlled, parallel group study to investigate the potential interaction between lamotrigine and olanzapine in healthy, nonsmoking male volunteers. Due to the relatively long half life ($T_{½}$) of lamotrigine at steady state (on average, 25 hours), the prolonged dose titration required to safely reach 200mg lamotrigine and the desire to estimate the potential interaction when both drugs are dosed to steady state, the parallel group design is favoured more than a crossover design. This was considered the most reliable design to provide answers to the pharmacokinetic questions that this study was investigating.

A total of 46 healthy male volunteers aged 18-55 years entered the study in three parallel cohorts. A screening assessment was performed up to 1 month prior to dosing with lamotrigine/placebo. Subjects were randomised in a 17:12:17 allocation ratio to receive lamotrigine and olanzapine, lamotrigine and placebo or placebo and olanzapine in three parallel arms. Lamotrigine was titrated from 25mg to 200mg per day according to the following recommended dose titration schedule:

Table 1. Dose Titration Regimen for Lamotrigine.

Dosing duration	Dose Lamotrigine (mg)
14 days	25
14 days	50
7 days	100
7 days	200

Cohort 1 received:

Lamotrigine 25mg during Days 1 to 14.
Lamotrigine 50mg during Days 15 to 28.
Lamotrigine 100mg during Days 29 to 35.
Lamotrigine 200mg during Days 36 to 56.
Olanzapine (15mg) during Days 43 to 56.

Cohort 2 received:

Lamotrigine 25mg during Days 1 to 14.
Lamotrigine 50mg during Days 15 to 28.
Lamotrigine 100mg during Days 29 to 35.
Lamotrigine 200mg during Days 36 to 56.
Olanzapine placebo during Days 43 to 56.

Cohort 3 received:

Lamotrigine 25mg-placebo during Days 1 to 14.
Lamotrigine 50mg-placebo during Days 15 to 28.
Lamotrigine 100mg-placebo during Days 29 to 35.
Lamotrigine 200mg-placebo during Days 36 to 56.
Olanzapine (15mg) during Days 43 to 56.

Olanzapine was titrated to a maximum dose level of 15mg in accordance with the following dose titration schedule:

Olanzapine was administered at 15mg dose according to the following titration protocols:
Day 1 5mg (evening dosing)
Day 2 10mg (evening dosing)
Day 3 15mg (evening dosing)
Day 4 no dose of olanzapine
Days 5-14 15mg (morning dose)

Cohort 1:

Cohort 1 comprised 17 volunteers who received lamotrigine titrated from 25mg to 200mg for 56 days. A total of 15mg olanzapine was added at Day 43 and this dose was taken for 14 days with the last dose taken on Day 56. On Day 56, steady state concentrations had been achieved for both drugs. The pharmacokinetic profile of lamotrigine and olanzapine was obtained on Day 56 over 24 hours.

Day 1-14 Lamotrigine 25mg
Day 15-28 Lamotrigine 50mg
Day 29-35 Lamotrigine 100mg
Day 36-42 Lamotrigine 200mg

Day 43 Lamotrigine 200mg + Olanzapine (5mg, administered at night)
Day 44 Lamotrigine 200mg + Olanzapine (10mg, administered at night)
Day 45 Lamotrigine 200mg + Olanzapine (15mg, administered at night)
Day 46 Lamotrigine 200mg only
Day 47-56 Lamotrigine 200mg + Olanzapine (15mg, administered on waking, i.e. on Day 47 the morning dose was 36 hour after last dose)

Cohort 2

Cohort 2 comprised 12 volunteers who received lamotrigine titrated from 25mg to 200mg for 56 days. Olanzapine placebo was added at Day 43 and this dose was taken for 14 days with the last dose taken on Day 56. On Day 56, steady state concentrations had been achieved for both drugs. The pharmacokinetic profile of lamotrigine and olanzapine was obtained on Day 56 over 24 hours.
Day 1-14 Lamotrigine 25mg
Day 15-28 Lamotrigine 50mg
Day 29-35 Lamotrigine 100mg
Day 36-42 Lamotrigine 200mg
Day 43 Lamotrigine 200mg + Olanzapine placebo (administered at night)
Day 44 Lamotrigine 200mg + Olanzapine placebo (administered at night)
Day 45 Lamotrigine 200mg + Olanzapine placebo (administered at night)
Day 46 Lamotrigine 200mg only
Day 47-56 Lamotrigine 200mg + Olanzapine placebo (administered on waking, i.e. on Day 47 the morning dose was 36 hour after last dose)

Cohort 3
Cohort 3 comprised 17 volunteers who received placebo for 56 days. Olanzapine (15mg) was added on Day 43 and this dose was taken for 14 days with the last dose taken on Day 56. The pharmacokinetic profile of olanzapine was obtained on Day 56 over 24 hours when a steady-state olanzapine concentration had been achieved.
Day 1-14 Lamotrigine 25mg placebo
Day 15-28 Lamotrigine 50mg placebo
Day 29-35 Lamotrigine 100mg placebo
Day 36-42 Lamotrigine 200mg placebo
Day 43 Lamotrigine 200mg placebo + Olanzapine (5mg, administered at night)
Day 44 Lamotrigine 200mg placebo + Olanzapine (10mg, administered at night)
Day 45 Lamotrigine 200mg placebo + Olanzapine (15mg, administered at night)
Day 46 Lamotrigine 200mg placebo only
Day 47-56 Lamotrigine 200mg placebo + Olanzapine (15mg, administered on waking, i.e. on Day 47 the morning dose was 36 hour after last dose).
The study included a screening assessment, a treatment period of 56 days and a follow-up assessment. Any subjects who discontinued from the study prematurely were not to be replaced.

A detailed time and events table is shown in Table 2.

Table 2. Time and events schedule.

SCA10908	Up to D-28	Study Days																	
	S	pd Day 1	8	15	22	29	36	43	44	45	46	47	48	49	50-53	54-55	56	57	F/U
Dosing of lamotrigine/placebo		←—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→		
Dosing of Olanzapine/placebo								←	—	—	—	—	—	—	—	—	→		
Phys exam/Med hist	X																		X
12 lead ECG	X																		X
Vitals standing & supine BP & HR[4]	X	X						X	X	X		X[4]	4	4	4	4	X[4]	X	X
Dematological assessment	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Lab screen	X	X						X									X		X
Liver Function Test								5	5	5	5	5	5	X	5	5	5	5	
Urine Drugs of Abuse[1]	X																		
Alcohol breath test	X	X	X	X	X	X	X	X											
PK Blood sampling																X	X[2]	X[2]	
Resident								←	—	—	—	—	—	—	—	—	—	→	
AE's[3]		←—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→	

1. Drugs of abuse was tested randomly throughout the study
2. 24-hour pharmacokinetic profile on day 56 (pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 & 24 hours)
3. Spontaneous reports of AE's were recorded throughout the study in addition to specific questioning on visit days
4. HR may have been monitored throughout the night and during all sleeping periods during the day
5. Liver function tests may have been repeated every other day

S =Screening · pd = pre-dose; F/U = follow up

Dose Rationale

The target dose of lamotrigine in two pivotal studies investigating the potential of lamotrigine to prevent the recurrence of bipolar episodes was 200mg/day. The proposed prescribing information recommends a dosing range of 100-400mg/day with a target dose of 200mg/day. A daily dose of 200mg was selected for this study because it is a clinically relevant dose that is considered tolerable in healthy volunteers. The proposed doses in this study follow the standard recommended dose titration schedule of lamotrigine used in clinical practice.

The recommended dose of olanzapine for treatment of mania is 5-20mg, adjusted on the basis of clinical status. The 15mg dose was preferred as this is the dose for which most of the efficacy data of olanzapine exists. As there was limited tolerability information on the 15mg dose in healthy subjects a separate small pilot tolerability study (SCA10911 GlaxoSmithKline Document Number HM2003/00020/00) was conducted prior to dosing olanzapine in this study.

Table 3. Demographic Characteristics for All subjects in Study SCA10908

Demographic Characteristic	Cohort 1 N=19	Cohort 2 N=13	Cohort 3 N=20
Age (Years)			
Mean (SD)	25 (4)	24 (6)	25 (3.6)
Range	20 - 34	18 – 42	20 – 33
Race, n (%)			
White	18 (95%)	12 (92%)	20 (100%)
Black	1 (5%)	1 (8%)	0
Height (cm)			
Mean (SD)	178 (5.7)	179 (6.1)	180 (6.5)
Range	165 – 186	164 – 189	170 – 191
Weight (kg)			
Mean (SD)	82.7 (12.02)	75.9 (9.33)	79 (10.21)
Range	61.3 – 101.0	62.1 – 94.1	64.2 – 102.4
BMI			
Mean (SD)	25.9 (3)	23.7 (2.2)	24.4 (2.6)
Range	21 – 29.8	18.8 – 27.2	19.8 – 29.9

Pharmacokinetic Analyses

Serum lamotrigine and plasma olanzapine concentration-time data for each subject were analysed separately by non-compartmental pharmacokinetic methods using WinNonlin† Professional Version 3.1. (Pharsight Corporation). Serum lamotrigine and plasma olanzapine concentration-time data were tabulated and graphically presented for each subject.

From the individual serum lamotrigine and plasma olanzapine concentration versus time curves and using the actual collection times recorded on each sampling occasion, the following serum lamotrigine and plasma olanzapine pharmacokinetic parameters were calculated for each subject:

The maximum observed concentration (C_{max}) and the time to reach C_{max} (t_{max}). The area under the concentration-time curve from zero time (pre-dose) to 24 hours post-dose, $AUC_{(0-24)}$, was determined by a combination of linear and logarithmic trapezoidal methods. The linear trapezoidal method was employed for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method was used for those arising from decreasing concentrations.

Summary statistics (arithmetic mean, N, standard deviation (SD), median, minimum, maximum and geometric mean were calculated for the pharmacokinetic parameters. Mean and median serum lamotrigine and plasma olanzapine concentration-time profiles were derived using individual concentrations at each nominal sampling time for each formulation.

Loge-transformed $AUC_{(0-24)}$ and C_{max} of lamotrigine, in the presence and absence of olanzapine, and loge-transformed $AUC_{(0-24)}$ and C_{max} of olanzapine, in the presence and absence of lamotrigine, were analysed separately by analysis of variance (ANOVA) fitting a term for regimen. Data from regimens A and B were used in the model for the effect of olanzapine on lamotrigine and from regimens A and C for the model of the effect of lamotrigine on olanzapine.

In order to investigate the effects of lamotrigine on olanzapine, point estimates and 90% confidence intervals were constructed for the differences in loge-transformed $AUC_{(0-24)}$ and C_{max} of olanzapine in the presence and absence of lamotrigine (A-C), using the residual variance from the ANOVA. These were back transformed to obtain the estimates for the ratio olanzapine+lamotrigine:olanzapine (A:C).
In order to investigate the effects of olanzapine on lamotrigine, point estimates and 90% confidence intervals were constructed for the differences in loge-transformed $AUC_{(0-24)}$ and C_{max} of lamotrigine in the presence and absence of olanzapine (A-B), using the residual variance from the ANOVA. These were then back transformed to obtain the estimates for the ratio olanzapine+lamotrigine:lamotrigine (A:B).

The pooled between-subject coefficient of variation were calculated for loge-transformed parameters where:
CV resid (%) = SQRT(exp(MSE)-1) x 100
where MSE is the residual error from the model.
Distributional assumptions underlying these analyses would be assessed by residual plots. Homogeneity of variance would be assessed by plotting the studentised residuals against the predicted values from the model, whilst normality would be examined by normal plots. If the assumptions were seriously violated then non-parametric methods would have been used to construct 90% confidence intervals, and statistical inference would have been based on these results.
Listings were generated and summary statistics were calculated by regimen for all pharmacokinetic parameters. Geometric means and between-subject coefficients of variation (CVb) were calculated for loge-transformed endpoints where:
geometric mean = exp (mean on log scale)

CVb (%) = SQRT[exp(sd2+1)] x 100
where sd is the standard deviation of the loge-transformed data.

Sample Collection and Handling

Bioanalytical Methods-Lamotrigine

Bioanalytical Procedures-

Studied Period: September 27, 2002-April 11, 2003

Olanzapine- February 4, 2003
April 11, 2003

The maximum study sample storage period from first blood draw (November 29, 2002) to last sample analysis (February 04, 2003) is 67 days. For second reception, the maximum study sample storage period from the first blood draw (March 17, 2003) to last sample analysis (April 11, 2003) is 25 days.

Lamotrigine-Assays were conducted from January 31, 2003-April 7, 2003.(a)
See appendix for explanation of stability data.

Assay Validation

Parameter	Lamotrigine	Olanzapine
Method	HPLC-MS/MS TURBOIONSPRAY	HPLC-MS/MS TURBOIONSPRAY
Freeze-thaw	3 CYCLES	3 CYCLES
Benchtop Stability at RT	3 DAYS	50 HOURS
Long term at –20° C	975 DAYS	69 DAYS
Recovery Low Med High	(b) (4)	

Plasma Analysis Results

Parameter	Lamotrigine	Olanzapine
Method	LC/MS/MS	HPLC/UV
Sensitivity/LOQ	4 ng/ml	0.5 ng/ml
Linearity (Standard curve samples)	4-4000 ng/ml	0.5-50 ng/ml
Quality Control (QC) Samples	12, 1600, 3200, 12000 ng/ml	1.5, 25, 37, 37.5 ng/ml
Precision of Standards (%CV)	7%@ 4 ng/ml 2.5%@ 4000 ng/ml	2% @ 0.5 ng/ml 2% @ 50 ng/ml
Precision of QC	4%@ 12 ng/ml	6% @ 0.5 ng/ml

Samples (%CV)	5%@ 3200 ng/ml	6% @ 50 ng/ml
Accuracy of Standards (%)	99%@ 4 ng/ml 98%@ 4000 ng/ml	102% @ 0.5 ng/ml 101% @ 50 ng/ml
Accuracy of QC Samples (%)	105%@ 12 ng/ml 99%@ 3200 ng/ml	100% @ 0.5 ng/ml 0.2% @ 50 ng/ml

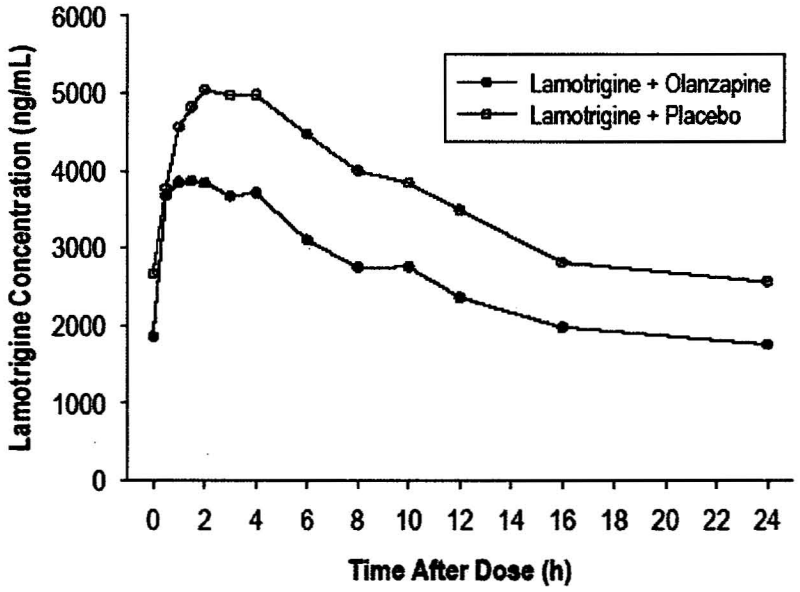
Statistical Analysis

RESULTS

Effect of Olanzapine on Lamotrigine pharmacokinetics

Median serum lamotrigine concentration-time profiles for lamotrigine in the presence and absence of olanzapine are displayed in Figure . Following lamotrigine administration with olanzapine or placebo, serum lamotrigine concentrations were quantifiable prior to dosing, and concentrations increased following dosing. Peak lamotrigine concentrations were observed between 0.5-4 hours post-dose and declined thereafter, but remained quantifiable for the entire 24-hour post-dose period.

Figure 1. Median serum lamotrigine concentration-time profiles



A summary of pharmacokinetic parameters for lamotrigine and corresponding statistical analyses are displayed in Table .

Table 4. Summary (geometric mean (range)) lamotrigine pharmacokinetic parameters and comparison between regimens

Parameter	Regimen A Lamotrigine + Olanzapine (N=16)	Regimen B Lamotrigine + Placebo (N=12)	Ratio (A:B) of Geometric Means (90% CI)	CV_b (%) (A+B)
C_{max} (ng/mL)	4285 (3038-6271)	5358 (4773-6226)	0.80 (0.71, 0.90)	18.7
$AUC_{(0-24)}$ (ng.h/mL)	66231 (43927-124533)	87166 (70660-108178)	0.76 (0.65, 0.90)	25.6
t_{max} (h)[1]	2.00 (0.50-4.00)	2.00 (1.00-4.00)	NA	

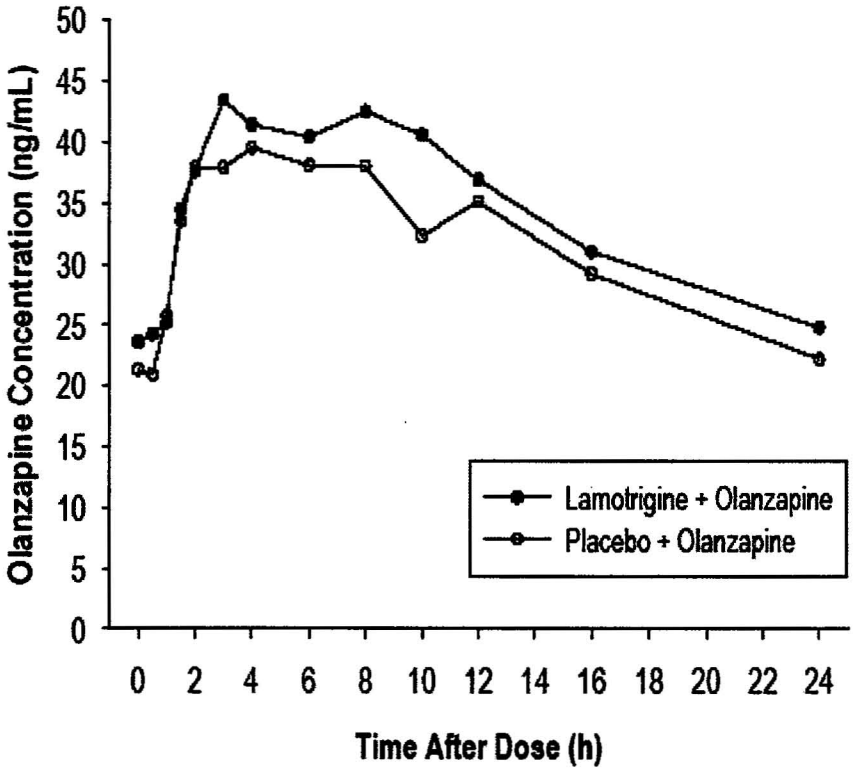
1. Median (range). NA = Not applicable

The point estimates provide the best estimate of the true value for the ratio and the corresponding confidence intervals provide a range of plausible values based on the data analysed. Lamotrigine $AUC_{(0-24)}$ and C_{max} were, on average, 24% and 20% lower, respectively, when lamotrigine was administered with olanzapine compared to lamotrigine and placebo. The 90% CI indicated that the true differences lie between 10% and 35% lower for $AUC_{(0-24)}$ and between 10% and 29% lower for C_{max}.

Effect of Lamotrigine on Olanzapine Pharmacokinetics

Median plasma olanzapine concentration-time profiles in presence and absence of lamotrigine are displayed in Figure 8. Following olanzapine administration with lamotrigine or placebo, plasma olanzapine concentrations were quantifiable prior to dosing, and concentrations increased after dosing. Peak olanzapine concentrations were observed between 1.5-8 hours post-dose and declined thereafter, but remained quantifiable for the entire 24-hour post-dose period.

Figure 2. Median plasma olanzapine concentration-time profiles



A summary of pharmacokinetic parameters for olanzapine and corresponding statistical analyses are displayed in Table .

Table 5. Summary (geometric mean (range)) olanzapine pharmacokinetic parameters and comparison between regimens

Parameter	Regimen A Lamotrigine + Olanzapine (N=16)	Regimen C Placebo + Olanzapine (N=16)	Ratio (A:C) of Geometric Means (90% CI)	CV_b (%) (A+C)
C_{max} (ng/mL)	45.9 (32.9-74.2)	44.4 (30.6-72.2)	1.03 (0.90, 1.19)	23.1
$AUC_{(0-24)}$ (ng.h/mL)	817 (606-1238)	786 (572-1267)	1.04 (0.90, 1.20)	23.7
t_{max} (h)[1]	3.06 (2.00-8.02)	4.00 (1.50-8.00)	NA	NA

1. Median (range). NA = Not applicable

The point estimates provide the best estimate of the true value for the ratio and the corresponding confidence intervals provide a range of plausible values based on the data analysed.

Olanzapine $AUC_{(0-24)}$ and C_{max} were similar when olanzapine was administered with lamotrigine compared to placebo.

Comments:

1. Lamotrigine $AUC_{(0-24)}$ and C_{max} were, on average, 24% and 20% lower, respectively, when lamotrigine was administered with olanzapine compared to lamotrigine and placebo. The 90% CI indicated that the true differences lie between 10% and 35% lower for $AUC_{(0-24)}$ and between 10% and 29% lower for C_{max}.

2. Olanzapine $AUC_{(0-24)}$ and C_{max} were similar when olanzapine was administered with lamotrigine, or placebo. The 90% CI indicated that the true differences lie between a 10% decrease and 20% increase for $AUC_{(0-24)}$ and between a 10% decrease and 19% increase for C_{max}.

SIGNATURES

Andre Jackson_____
Reviewer, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FT initialized by Ray Baweja, Ph.D..._____
Team Leader, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

cc: NDA HFD-120, HFD-860(Mehta, Rahman, Baweja, Jackson)

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APPENDIX

Long term olanzapine plasma stability (SCA10908)

Samples were received at Anapharm on 08-Jan-03 and 26-Mar-03 and stored at -80°C.

1. For the samples received on 08-Jan-03, the maximum study sample storage period from the first blood draw (29-Nov-02) to last sample analysis (04-Feb-03) was 67 days.
2. For the samples received on 26-Mar-03, the maximum study sample storage period from the first blood draw (17-Mar-03) to last sample analysis (11-Apr-03) was 25 days.

The stability data presented in the assay validation report for olanzapine in human K3EDTA plasma at -80°C is 69 days, covering the maximum storage period of the samples prior to analysis.

APPENDIX VI-ORAL CONTRACEPTIVES

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG:LAMOTRIGINE **PRIMARY REVIEWER**: Andre Jackson
NDA:20241 **TYPE: Labeling Supplement**

FORMULATION:Tablet **STRENGTH: 100 mg/day -400 mg/day**
APPLICANT:Glaxo Smith Kline Submission Date: August 11, 2004

INDICATIONS:Anti-Epileptic
Generic Name: Lamictal

Drug –Drug Interaction Study LAM10016-Lamotrigine and Oral Contraceptives

Introduction

Women with epilepsy have specific gender issues related to epilepsy itself as well as its treatment options . These issues include disturbances in fertility, menstrual cyclicity and ovulatory function associated with epilepsy, and the use of hormonal contraception in combination with common anti-epileptic medication.
With respect to the latter issue, the co-prescription of anti-epileptic medication and oral contraceptives may be associated with problems for two reasons. Firstly, anticonvulsants may decrease the efficacy of oral contraceptives because of the hepatic enzyme-inducing properties of many anticonvulsants . Any drug interaction that increases clearance or reduces absorption of the contraceptive components (synthetic oestrogen and a progestogen), may have an impact on the efficacy of the contraceptives. Secondly, oral contraceptives may reduce the efficacy of anticonvulsants, again through enzyme induction. A clear understanding of the potential interaction between oral contraceptives and anticonvulsants is therefore important and is the basis of the proposed bidirectional study.
Use of oral contraceptives can increase the metabolism of glucuronidated drugs by induction of glucuronide-conjugating enzymes. Lamotrigine is metabolised in the liver primarily by glucuronic acid conjugation. Recent case reports of increased seizure frequency/recurrence of seizures after oral contraceptives had been introduced, or adverse events following withdrawal of oral contraceptives suggest possible effects of oral contraceptives on the efficacy and elimination of lamotrigine . These observations support the need to investigate whether OC administration affects the pharmacokinetics of lamotrigine and whether any interaction is of clinical relevance. A clear understanding of the effect of oral contraceptives on lamotrigine will ensure the safe and effective use of lamotrigine in this population.

The aim of this study was to investigate whether there is any effect of an OC upon lamotrigine or any effect of lamotrigine upon an OC.

STUDY OBJECTIVES

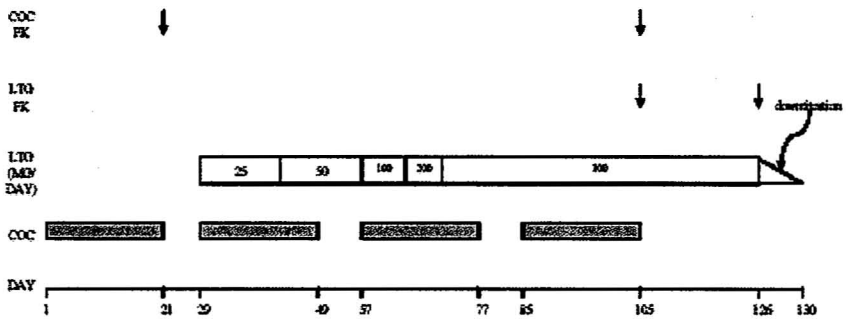
• To investigate the effects of the OC pill on the pharmacokinetics (PK) of lamotrigine when dosed to steady state.
• To investigate the effects of repeated doses of lamotrigine on the pharmacokinetics (PK) of the OC pill.

Overall Study Design – Description

This was an open, non-randomised, non-placebo-controlled, single sequence study conducted in 22 healthy young female subjects. The study included a screening evaluation, a treatment period of 130 days and a follow-up evaluation.

The study was begun on 26 June 2003 and was completed on 19 December 2003.

The design of the study is summarised in the diagram below:



Day 1 of the study was defined as the first day of Microgynon 30 after enrolment into the study. Subjects took Microgynon 30 in accordance with standard prescribing information, i.e. on a once-daily basis for 21 days (to be administered in the morning), followed by a 7-day, pill-free period. On Day 21 of the study, subjects underwent PK profiling for ethinyloestradiol and levonorgestrel. After the 7-day, pill-free interval,

subjects restarted the COC on Day 29 and also started lamotrigine at a dose of 25 mg once daily (to be administered in the morning). Subjects received lamotrigine at doses titrated from 25 mg per day to 300 mg per day, in accordance with the recommended dose-titration schedule, and continued to receive Microgynon 30 in accordance with standard prescribing information (21 days of treatment followed by a 7 day pill-free interval).

On Day 105 of the study, when subjects were on Day 21 of a COC cycle, PK profiling for ethinyloestradiol, levonorgestrel and lamotrigine was performed.

Subjects discontinued the COC on Day 105, but continued to take lamotrigine 300 mg once daily in the morning for a further three weeks (which allowed for a waning of any effect of the COC on glucuronidation systems plus a re-establishment of steady-state conditions for lamotrigine). Microgynon 30 was not taken during this three week period. On Day 126, PK profiling for lamotrigine was performed.

Additional predose PK samples were taken on Days 19, 20, 103, 104, 108, 110, 112, 124 and 125.

On Day 127, subjects reduced their dose of lamotrigine to 200 mg once daily, and continued to reduce their dose of lamotrigine by 100 mg every two days; the last day of study drug administration was Day 130.

On PK profiling Days 21, 105 and 126, subjects attended the Unit in the morning, where they took their dose following the predose blood sample. Subjects remained in-house on those days until the blood sample at 24 h postdose had been taken.

Additional blood samples were taken for measurements of follicle-stimulating hormone (FSH), luteinising hormone (LH), oestradiol, sex hormone binding globulin (SHBG) and progesterone levels during the study.

Within one week of the final dose of study medication, subjects returned for a follow-up assessment. After this follow-up visit subjects may or may not have restarted the COC of their choice, in accordance with advice from their medical practitioner.

Study Design, Including the Choice of Control Groups

The study was designed so that PK profiles of the OC alone were taken prior to starting lamotrigine and after up-titration of lamotrigine to reach the maximum dose level (300 mg daily) for 21 days. Lamotrigine PK parameters were assessed whilst the subject was taking OC and after a 3-week OC-free washout period. There were no control groups in this non-randomised, open-label study.

Investigational Products

Lamotrigine Immediate Release (IR) was supplied as chewable/dispersible 25 mg and 100 mg tablets.

Microgynon 30 was supplied as ethinyloestradiol 30 ug/levonorgestrel 150 micrograms,

Dosages and Administration

All subjects received a once-daily dose of lamotrigine according to the dose-titration regimen and description below, from Day 29 until Day 130.

Day 1 of the study was defined as the first day of Microgynon 30 after enrolment into the study. Subjects took Microgynon 30 in accordance with standard prescribing information on a once-daily basis for 21 days (to be administered in the morning), followed by a 7-day, pill-free period. After a 7-day, pill-free interval, subjects restarted the OC (Microgynon 30) on Day 29 and also started lamotrigine at a dose of 25 mg once daily (to be administered in the morning). Subjects received lamotrigine at doses titrated from 25 mg per day to 300 mg per day in accordance with the recommended dose-titration schedule, and continued to receive Microgynon 30 in accordance with standard prescribing information (21 days of treatment followed by a 7 day pill-free interval). Subjects discontinued taking the OC on Day 105, but continued to take lamotrigine 300 mg once daily in the morning for a further three weeks; Microgynon 30 was not taken during this three-week period.
On Day 127, subjects reduced their dose of lamotrigine to 200 mg once daily, and continued to reduce their dose of lamotrigine by 100 mg every two days; the last day of study drug administration was Day 130.

Dose Rationale

Microgynon 30 is one of the most commonly prescribed, low dose combined oral contraceptives in Europe. It provides good cycle control with minimal side effects and it is recommended due to the reduced risk of venous thromboembolism in comparison to third generation preparations. It was expected that using this common pill would provide data representative of second generation OCs and, due to its prevalence, volunteers already established on this pill would not have to switch prior to entering the study. Microgynon 30 provides 150 ug levonorgestrel and 30 ug ethinyloestradiol, taken as an oral tablet for the first three weeks of each menstrual cycle.

Subjects received lamotrigine at doses titrated from 25 mg to 300 mg per day in accordance with the recommended dose-titration schedule. This stepwise titration schedule has been established to reduce the risk of the development of rash.

The protocol on the effect of lamotrigine on the PK of the components of Microgynon 30 would be limited to a 300 mg dose of lamotrigine.

Collection of samples

For assessment of levonorgestrel and ethinyloestradiol PK, plasma levels were measured from blood samples (approx. 8 mL each) at predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 h postdose on Days 21 and 105 of treatment.

For assessment of lamotrigine PK, serum levels were measured from blood samples (approx. 2 mL each) drawn at predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 h postdose on Days 105 and 126 of treatment.

Additional predose PK samples were taken to assess achievement of steady state concentrations of levonorgestrel and ethinyloestradiol (approx. 8 mL each) on Days 19, 20, 103 and 104 and of lamotrigine (approx. 2 mL each) on Days 103, 104, 124 and 125.

Predose PK samples were also taken to assess the effect of tapering OC concentrations on lamotrigine disposition (on Days 108, 110, 112).

On PK profiling Days 21, 105 and 126, subjects attended the Unit in the morning, where they took their dose following the predose blood sample.

Treatment Comparisons

The primary comparisons of interests were:

- Lamotrigine + OC compared with lamotrigine alone, and
- Lamotrigine + OC compared with OC alone.

The primary endpoints were steady-state C_{max} and $AUC_{(0-24)}$ of lamotrigine in the presence and absence of ethinyloestradiol and levonorgestrel of OC, and steady-state C_{max} and $AUC_{(0-24)}$ of ethinyloestradiol and levonorgestrel of OC in the presence and absence of lamotrigine.

Secondary PK endpoints were t_{max} of lamotrigine in the presence and absence of ethinyloestradiol and levonorgestrel of OC, and t_{max} of ethinyloestradiol and levonorgestrel of OC in the presence and absence of lamotrigine.
Safety parameters were adverse events and clinically relevant changes in clinical

For $AUC_{(0-24)}$ and C_{max} of lamotrigine, ethinyloestradiol and levonorgestrel the following summary statistics were calculated for each treatment group: median, minimum, maximum, arithmetic mean, 95% confidence interval (CI) for the arithmetic mean, standard deviation (SD), coefficient of variation (calculated as %CVb = 100*(SD/Mean)), geometric mean, 95% CI for the geometric mean and standard deviation of logarithmically transformed data. For t_{max}: median, minimum, maximum, arithmetic mean, 95% confidence interval for the arithmetic mean, standard deviation and coefficient of variation were calculated.

Following $\log_e$ transformation, the $AUC_{(0-24)}$ and C_{max} for lamotrigine were analysed separately by analysis of variance (ANOVA), fitting session as a fixed effect term and subject as a random effect. Point estimates and 90% CIs for the differences between lamotrigine + OC compared with lamotrigine alone were constructed using the residual variance from the ANOVA. These were then exponentially back-transformed to obtain the estimates of the ratio of geometric means and 90% CI for lamotrigine + OC : lamotrigine alone. Lack of a clinically-relevant effect of OC on lamotrigine using an equivalence approach (two, one-sided t-tests expressed as a 90% CI) for the lamotrigine endpoints was demonstrated if the 90% CI was completely contained within the acceptance range (b) (4)).

Following $\log_e$ transformation, the $AUC_{(0-24)}$ and C_{max} for ethinyloestradiol and levonorgestrel were analysed separately by ANOVA, fitting session as a fixed effect term and subject as a random effect. Point estimates and 90% CIs for the differences between lamotrigine + OC compared with OC alone were constructed using the residual variance from the ANOVA. These were then exponentially back-transformed to obtain the estimates of the ratio of geometric means and 90% CI for lamotrigine + OC : OC

alone. Lack of a clinically relevant effect of lamotrigine on OC using an equivalence approach (two, one-sided t-tests expressed as a 90% CI) for the OC endpoints would be demonstrated if the 90% CI was completely contained within the acceptance range ((b) (4)).
Within-subject CV for $AUC_{(0-24)}$ and C_{max} of lamotrigine, levonorgestrel and ethinyloestradiol were calculated based on the $\log_e$-Normal distribution:

$CV_w(\%) = \text{sqrt}[\exp(\text{mse}) - 1] \times 100$
where mse was the residual error from the relevant model.
Assumptions underlying the analyses were assessed by inspection of residual plots. Homogeneity of variance was assessed by plotting the studentised residuals against the predicted values from the model, whilst Normality was assessed by use of Normal probability plots. If the assumptions were seriously violated then non-parametric methods would have been used.

Formal proof of steady-state was not critical but an analysis of steady state was performed for lamotrigine, levonorgestrel and ethinyloestradiol.
To evaluate whether steady state was achieved, statistical analysis of predose ("trough") concentration levels were performed after a $\log_e$ transformation of the data. For lamotrigine, analysis was performed on Days 103, 104 and 105 predose and Day 105 at 24 h postdose, and, separately, for Days 124, 125 and 126 predose and Day 126 at 24 h postdose. For levonorgestrel and ethinyloestradiol separate analyses were performed for Days 19, 20, 21 predose and Day 21 at 24 h postdose and then for Days 103, 104, 105 predose and Day 105 at 24 h postdose. Separate mixed-effect models were fitted with day as a fixed-effect continuous covariate and subject as a random effect.
The coefficient of the slope of the day-effect on the $\log_e$ scale was calculated to evaluate whether steady state was achieved in each analysis. Using the pooled estimate of variance, the 90% CIs for the slope was calculated and then back-transformed to the original scale. Statistical confirmation of steady state was reached if the 90% CI limits were within the range of 0.91-1.10.
Predose serum lamotrigine concentrations determined on Days 108, 110 and 112 (i.e., during the "pill-free week") were also summarised statistically and were expressed as a percentage (both at an individual and group level) of average predose serum lamotrigine concentrations on Days 103 to 105 and of the average on Days 124 to 126.

Analytical

Lamotigine
Study Dates: Began on 26 June 2003 and was completed on 19 December 2003.

Sample Assay Dates: Assayed between 23 to 28 January 2004

Total Storage time: ~210 days

Ethinyloestradiol and Levonorgestrel:

Study Dates: Began on 26 June 2003 and was completed on 19 December 2003.

Sample Assay Dates: Assayed between February 4, 2004-February 10, 2004.

Total Storage time: ~240 days

Assay Validation

Parameter	Lamotrigine	Ethinyloestradiol *	Levonorgestrel*
Method	HPLC-MS/MS TURBOIONSPRAY	HPLC-MS/MS TURBOIONSPRAY	HPLC-MS/MS TURBOIONSPRAY
Freeze-thaw	3 CYCLES	6 CYCLES	5 CYCLES
Benchtop Stability at RT	3 DAYS	46 HOURS	46 HOURS
Long term at –20° C	975 DAYS	11 MOS	696 DAYS
Recovery Low Med High	(b) (4)		

- *Recovery data not supplied by the firm.
-

Plasma Analysis Results

Parameter	Lamotrigine	Ethinyloestradiol	Levonorgestrel
Method	LC/MS/MS	HPLC/MS/MS	HPLC/MS/MS
Sensitivity/LOQ	4 ng/ml	2.0 pg/ml	50 pg/ml
Linearity (Standard curve samples)	4-4000 ng/ml	2-500 pg/ml	50-25000pg/ml
Quality Control (QC) Samples	12, 1600, 3200, 12000 ng/ml	5, 50, 400 pg/ml	125, 1250, 20000 pg/ml
Precision of Standards (%CV)	7%@ 4 ng/ml 2.6%@ 4000 ng/ml	10% @ 2.0 pg/ml 2.5% @ 500 pg/ml	9% @ 50 pg/ml 2.8% @ 25000 pg/ml
Precision of QC Samples (%CV)	7%@ 12 ng/ml 4%@ 3200 ng/ml	5% @ 5 pg/ml 4% @ 400 pg/ml	20% @ 125 pg/ml 3% @ 20000 pg/ml

Accuracy of Standards (%)	99%@ 4 ng/ml 97%@ 4000 ng/ml	99.4% @ 2.0 pg/ml 95% @ 500 ng/ml	99.7% @ 50 pg/ml 93% @ 25000 pg/ml
Accuracy of QC Samples (%)	100%@ 12 ng/ml 95%@ 3200 ng/ml	98.8 @ 5 pg/ml 97% @ 400 pg/ml	97 @ 125 pg/ml 89% @ 20000 pg/ml

RESULTS

Table 1. Demographic Characteristics of Study Population (N = 22)

	Age [years]	Weight [kg]	Height [cm]	Body Mass [kg/m²]
Mean	31.0	67.1	167	24.0
(range)	(19 - 45)	(53.0 - 84.0)	(157 – 180)	(19.5 - 29.4)

Effect of OC on Lamotrigine Pharmacokinetics

Median serum lamotrigine concentration-time profiles for lamotrigine in the presence and absence of OC are displayed in Figure 1. The secondary PK endpoint, t_{max} for lamotrigine, was between 0.5 h and 4 h postdose, irrespective of regimen. Systemic lamotrigine exposure, however, was substantially reduced in the presence of the OC. Although elimination half-lives were not derived (as PK sampling was only over approximately one half-life for lamotrigine at steady state), the semi-log profiles in Figure 1 indicate an increase in the rate of lamotrigine elimination by the OC.

Figure 1 Median Serum Lamotrigine Concentration-Time Profiles

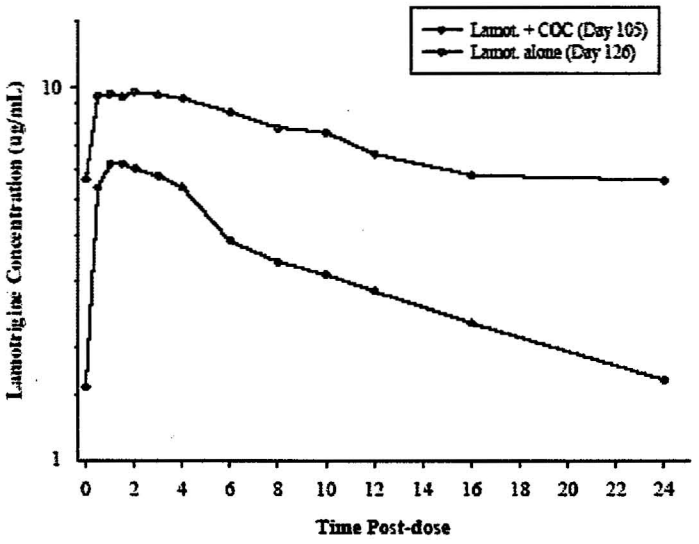


Table 2. Summary lamotrigine pharmacokinetic parameters and comparison between regimens (n = 16)

Comparison (Test : Reference)	Parameter	Geometric LS[a] mean (lamotrigine + COC)	Geometric LS mean (lamotrigine)	Ratio	90% CI
lamotrigine + COC : lamotrigine alone	Lamotrigine $AUC_{(0\text{-}24)}$ (ug.h/mL)	78.8	163	0.48	(0.44, 0.53)
	Lamotrigine C_{max} (ug/mL)	6.33	10.3	0.61	(0.57, 0.66)

For lamotrigine $AUC_{(0\text{-}24)}$ and C_{max}, the 90% CIs of the ratios lamotrigine + OC : lamotrigine alone lay completely outside of the acceptance range (b) (4) , indicating a clinically relevant effect of OC. For lamotrigine $AUC_{(0\text{-}24)}$ there was, on average, a decrease of 52% when administered with OC, with an indication that the true decrease lay between 47% and 56%. For lamotrigine C_{max}, there was an average decrease of 39% when administered with OC, with an indication that the true decrease lay between 34% and 43%. The average 52% decrease in lamotrigine $AUC_{(0\text{-}24)}$ translates to an approximate 2.1-fold increase in lamotrigine apparent clearance in the presence of OC.

A stepped and notable rise in predose serum lamotrigine concentrations was observed during the "pill-free" week (Days 106 to 112), with concentrations by Day 112 being, on average, approximately 2-fold higher than during the OC co-administration period (Table 3). De-induction of lamotrigine clearance was incomplete by the end of the "pill-free week" with predose lamotrigine concentrations on Day 112 being, on average, approximately 80% of those achieved during the lamotrigine monotherapy period (Days 124 to 126).

Table 3. Mean (Range) of Individual Ratios of Predose Serum Lamotrigine Concentrations During the "Pill-free Week" Relative to OC Coadministration or During Lamotrigine Monotherapy[a] (n = 15)

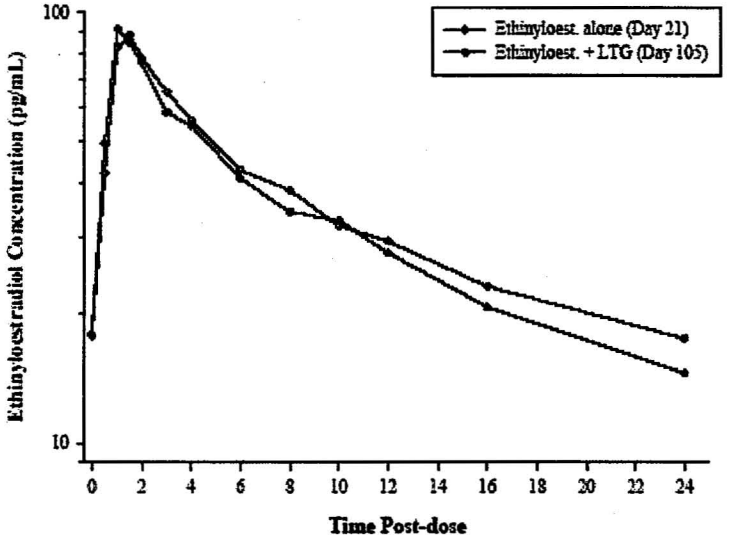
	Co-Admin Period[a]	Monotherapy Period[b]
Day 108	1.27 (0.92-1.63)	0.47 (0.21-0.84)
Day 110	1.63 (2.58-2.17)	0.60 (0.16-0.88)
Day 112	2.16 (1.39-2.94)	0.77 (0.47-0.98)

Data source: Section 14, Table 14.25.
a. "Co-administration" = av. of Days 103 to 105 predose concentrations
b. "Monotherapy" = av. of Days 124 to 126 predose concentrations.
Days 108, 110 & 112 = Days 3, 5 & 7 of "pill-free week", respectively.

Effect of Lamotrigine on OC Pharmacokinetics

Median plasma ethinyloestradiol and levonorgestrel concentration-time profiles for OC in the presence and absence of lamotrigine are displayed in Figure 2. Peak concentrations were observed between 1 h and 3 h postdose for ethinyloestradiol and 0.5 h and 3 h postdose for levonorgestrel, irrespective of regimen.

Figure 2 **Median Plasma Ethinyloestradiol and Levonorgestrel Concentration-Time Profiles**



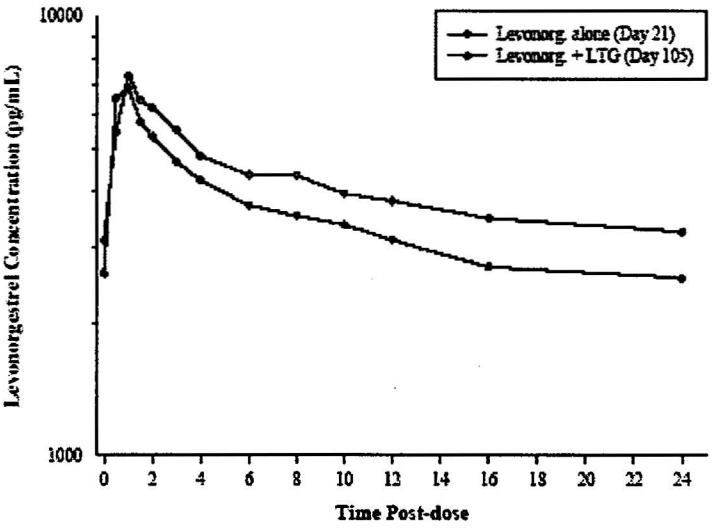


Table 4. Comparison between Regimens for Primary Pharmacokinetic Parameters for Ethinyloestradiol and Levonorgestrel (n = 16)

Comparison (Test:Reference)	Parameter	Geometric LS[a] mean (lamotrigine + COC)	Geometric LS mean COC	Ratio	90% CI
lamotrigine + COC: COC alone	Ethinyloestradiol $AUC_{(0-24)}$ (pg.h/mL)	785	849	0.93	(0.88, 0.97)
	Ethinyloestradiol C_{max} (pg/mL)	91.7	89.5	1.02	(0.95, 1.10)
lamotrigine + COC: COC alone	Levonorgestrel $AUC_{(0-24)}$ (pg.h/mL)	79981	98653	0.81	(0.76, 0.86)
	Levonorgestrel C_{max} (pg/mL)	6886	7858	0.88	(0.82, 0.93)

Data source: Section 14, Table 14.15, Table 14.18, Table 14.19, Table 14.20 and table 14.21
a. LS = least squares

For both ethinyloestradiol and levonorgestrel $AUC_{(0-24)}$ and C_{max}, all the 90% CIs of the ratio lamotrigine + COC : COC alone lay completely inside of the acceptance range(b) (4)

On average, ethinyloestradiol $AUC_{(0-24)}$ decreased 7% and C_{max} increased 2% when administered with lamotrigine, with the 90% CIs indicating that the true decrease lies between a decrease of 3% and 12% for $AUC_{(0-24)}$ and between a decrease of 5% and an increase of 10% for C_{max}. For levonorgestrel, $AUC_{(0-24)}$ and C_{max}, respectively, decreased by 19% and 12% when administered with lamotrigine, with the 90% CIs indicating that the true decrease lies between a decrease of 14% and 24% for $AUC_{(0-24)}$ and between a decrease of 7% and 18% for C_{max}.

Analysis of Steady State

The analysis of achievement of steady state of lamotrigine, ethinyloestradiol and levonorgestrel using predose serum/plasma concentrations is summarised in Table 5.

Table 5. Summary of Statistical Analysis of Steady State

Analysis	Slope (back-transformed)	90% CI (back-transformed)
Lamotrigine Days 103 to 106	0.99	(0.96,1.02)
Lamotrigine Days 124 to 127	0.99	(0.97,1.01)
Levonorgestrel Days 19 to 22	0.98	(0.96,1.00)
Levonorgestrel Days 103 to 106	0.98	(0.96,1.00)
Ethinyloestradiol Days 19 to 22	0.95	(0.92, 0.98)
Ethinyloestradiol Days 103 to 106	0.93	(0.91, 0.95)

Data source: Section 14, Table 14.13.

As all the slopes and the 90% CI limits were within the range 0.91-1.10, steady-state of lamotrigine, ethinyloestradiol and levonorgestrel was statistically confirmed.

COMMENTS:

- There was a clinically relevant effect of Microgynon 30 on the pharmacokinetics of lamotrigine, resulting in an average 52% and 39% decrease in lamotrigine $AUC_{(0\text{-}24)}$ and C_{max}, respectively.
- Predose serum lamotrigine concentrations increased in a fairly rapid manner during the "pill-free week", with concentrations at the end of this week being, on average, approximately 2-fold higher than during Microgynon 30 co-administration. However, complete de-induction of lamotrigine clearance was not attained by the end of the "pill-free week".
- Lamotrigine had a minimal effect on ethinyloestradiol pharmacokinetics and caused a modest reduction in levonorgestrel exposure (an average 19% and 12% decrease in $AUC_{(0\text{-}24)}$ and C_{max}, respectively).

SIGNATURES

Andre Jackson_____
Reviewer, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FT initialized by Ray Baweja, Ph.D..._____
Team Leader, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

cc: NDA 20241 , HFD-120, HFD-860(Mehta, Rahman, Baweja, Jackson)

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

/s/

Andre Jackson
11/17/2005 09:01:23 AM
BIOPHARMACEUTICS

Raman Baweja
11/17/2005 02:41:52 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-241/S-027 and 20-764/S-020

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 20-241 and 20-764 SUPPL # 027 and 020 HFD#120

Trade Name Lamictal

Generic Name lamotrigine tablets and chewable dispersible tablets

Applicant Name GSK

Approval Date, If Known 09-26-06

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

LAM40097 A Multi-Center, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Evaluation of Lamotrigine Adjuctive Therapy in Subjects with Primary Generalized Tonic-Clonic Seizures.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

LAM40097 A Multi-Center, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Evaluation of Lamotrigine Adjuctive Therapy in Subjects with Primary Generalized Tonic-Clonic Seizures.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # 43,551
YES ☒ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:
NA	

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:
NA	

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

Name of person completing form: Courtney Calder
Title: Project Manager
Date: October 12, 2006

Name of Office/Division Director signing form: Rusty Katz, MD
Title: Divison Director
Division of Neurology Products

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

/s/

Russell Katz
10/12/2006 03:26:25 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

CLINICAL INSPECTION SUMMARY

DATE: 9/13/05

TO: Courtney Calder, Pharm.D., Regulatory Health Project Manager
Philip Sheridan, M.D., Medical Officer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Ni Khin, M.D., Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations, HFD-46

FROM: Robert S. Stasko, M.D., Medical Officer
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA#: 20-241/SE1-027, NDA#: 20-764/SE1-020

RE: Drug: Lamotrigine (Lamictal ®)
Chemical Classification: 6 / Standard Review
Sponsor: GSK
Protocol: LAM40097-SPECTRUM
Indication: adjunctive treatment of primary generalized tonic-clonic (PGTC) seizures

CONSULTATION REQUEST DATE: 5/26/05

PDUFA DATE: 12/7/05

I. BACKGROUND:

In the U.S., lamotrigine is approved as adjunctive therapy in adults with partial seizures and as adjunctive therapy in pediatric and adult patients with the generalized seizures of Lennox-Gastaut syndrome. Lamotrigine is also approved for conversion to monotherapy in adults with partial seizures who are receiving treatment with a single enzyme-inducing anti-epileptic drug (e.g., carbamazepine). This current application included the results from the pivotal protocol LAM40097-SPECTRUM, “A Multi-Center, Double-blind, Randomized, Placebo-Controlled,

Parallel-Group Evaluation of Lamotrigine Adjunctive Therapy in Subjects with Primary Generalized Tonic-Clonic Seizures [Date from the Double Blind]", to pursue an additional new indication for the adjunctive treatment of primary generalized tonic-clonic seizures in both children and adults.

Protocol: LAM40097-SPECTRUM

This study was a Phase-IV, international, multi-center, double-blind, randomized, placebo-controlled, parallel-group study. This trial consisted of a Screen and 3 Phases (i.e., Baseline, Dose Escalation, Maintenance) lasting 32 weeks for subjects who are 2-12 years of age, and 27 weeks for subjects who are >12 years of age. Subjects 2-12 years of age had a longer dose escalation phase than subjects >12 years of age to reach their target maintenance dose. All randomized subjects who complete the Maintenance Phase or withdraw prematurely from the study treatment due to exacerbation of their seizure activity or intolerable, but not medically serious, side effects were offered the option to participate in an open-label Continuation Phase for a long-term follow up and receive open-label lamotrigine, if clinically appropriate, for up to 1 year (52 weeks). Subjects who fail to meet the minimum number of PGTC (primary generalized tonic-clonic) seizures during the prospective Baseline Phase will be allowed to enroll in the open-label Continuation Phase, if clinically appropriate, for up to 5 months. The study included subjects who are ≥ 2 years of age and ≥ 13kg with a diagnosis of epilepsy. Subjects must have an EEG consistent with PGTC seizures, with no evidence of interictal expression of partial seizures or other significant findings that are inadequately controlled with a stable regimen of 1 or 2 anti-epileptic drug(s) (AED). The primary objective was to assess the efficacy of lamotrigine adjunctive therapy in adult and pediatric subjects with primary generalized tonic-clonic (PGTC) seizures. The primary efficacy endpoint was the percentage change from Baseline in average monthly PGTC seizure frequency.

These 2 sites were chosen because of high enrollment. Dr. Biton had been inspected by the FDA once prior in 1999 (NAI); he is associated with (b) (4) INDs in COMIS. Dr. Tabbaa had never been inspected. He is associated with (b) (4) INDs in COMIS.

II. RESULTS (by site):

NAME	Protocol LAM40097 (Center)	Location	ASSIGNED DATE	DATE EIR RECEIVED	CLASSIFICATION
Dr. Victor Biton	#10369	Little Rock, AR	5/26/05	8/10/05	NAI
Dr. Mutaz Tabbaa	#24016	Panama City, FL	5/26/05	8/17/05	NAI

1. Dr. Victor Biton

a. What was inspected: At this site, 19 subjects were screened and 11 completed the trial. All 19 study subjects' source records and CRFs were reviewed. All inclusion/exclusion criteria appeared to be properly applied. All raw seizure counts were in agreement with data found in CRF and data listings. All subjects signed the informed consent form.

b. Limitations of inspection: none

c. General observations/commentary: No objectionable findings were found.

d. Recommendation: Overall, data would appear acceptable.

2. Dr. Mutaz Tabbaa

a. What was inspected: At this site, a total of 15 subjects were screened and 11 subjects enrolled. All subjects signed the informed consent form. Case report forms and files were reviewed for all 11 subjects enrolled. Eight were randomized with 1 subject withdrawing consent, 2 failing to meet inclusion/exclusion criteria. Six out of 8 randomized subjects received test article; 2 did not receive treatment due to a rash prior to treatment and one case of non-compliance. One of these six subjects was removed due to a protocol violation. Five successfully completed the trial.

c. Limitations of inspection: none

c. General observations/commentary: There were no objectionable conditions.

d. Recommendation: Overall, data would appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For the two study sites that were inspected for protocol LAM40097, there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, and that all enrolled subjects received the assigned study medication. Overall, data from these centers appear acceptable for use in support of this supplemental NDA.

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Robert S. Stasko, M.D., Medical Officer
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

_____

Ni Khin, M.D, Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations.
VAI-RR= Deviation(s) form regulations, response received and reviewed.
OAI = Significant deviations from regulations.
Pending = Inspection completed; EIR still pending

cc:
NDA#: 20-241/SE1-027, NDA#: 20-764/SE1-020
HFD-45/Division File/Reading File
HFD-45/Program Management Staff (electronic copy)
HFD-46/Khin(9/12/05)
HFD-46/Patague/GCPB1 Files
rd:RSS/(9/9/05), (9/13/05)

O:Stasko\CIS\CIS N20241 N20764 Drs.Tabbaa&Biton (NAI) LTG PGTC 9.05.doc

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/s/

Robert S. Stasko
9/13/2005 01:45:00 PM
MEDICAL OFFICER

Ni Aye Khin
9/19/2005 05:07:32 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:			FROM:	
HFD- 357			HFD-120/ Division of Neuropharmacological Drug Products	
DATE March 31, 2005	IND NO.	NDA NO. NDA 20-241/S-027 NDA 20-764/S-020	TYPE OF DOCUMENT Environmental Assessment in NDA supplement	DATE OF DOCUMENT February 4, 2005

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Lamictal (lamotrigine) tablets and chewable dispersible tablets			**Primary reviewer due date is 10/19/05.** **User fee due date is 12/07/05**

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
This is a SE1 supplement for Lamictal tablets and chewable dispersible tablets. It is located in the EDR at:: \\CDSESUB1\N20764\S_020\2005-02-04 or \\CDSESUB1\N20241\S_027\2005-02-04

Please review the environmental assessment and provide comments as appropriate. Let me know if anything is unclear. Thank you! Courtney

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Courtney Calder, Pharm.D. Regulatory Project Manager 301-594-5528 calderc@cder.fda.gov	☐ MAIL X HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Courtney Calder
3/31/05 06:57:17 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:			FROM:	
HFD- 005 ORP/DRPI			HFD-120/ Division of Neuropharmacological Drug Products	
DATE March 31, 2005	IND NO.	NDA NO. NDA 20-241/S-027 NDA 20-764/S-021	TYPE OF DOCUMENT Environmental Assessment in NDA supplement	DATE OF DOCUMENT February 4, 2005
NAME OF DRUG Lamictal (lamotrigine) tablets and chewable dispersible tablets	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE **Primary reviewer due date is 10/19/05.** **User fee due date is 12/07/05**

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

I. GENERAL

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- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
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- ☐ PRE-NDA MEETING
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- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
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- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
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V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
This is a SE1 supplement for Lamictal tablets and chewable dispersible tablets. It is located in the EDR at:: \\CDSESUB1\N20764\S_020\2005-02-04 or \\CDSESUB1\N20241\S_027\2005-02-04

Please review the environmental assessment and provide comments as appropriate. Let me know if anything is unclear. Thank you! Courtney

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Courtney Calder, Pharm.D. Regulatory Project Manager 301-594-5528	☐ MAIL X HAND

calderc@cder.fda.gov	
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/s/

Courtney Calder
3/31/05 06:37:52 PM

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	20-241	Brand Name	Lamictal
OCPB Division (I, II, III)	I	Generic Name	Lamotrigine
Medical Division	Neuropharmacology	Drug Class	
OCPB Reviewer	Andre Jackson	Indication(s)	Anti-epileptic
OCPB Team Leader(Acting)	Sally Yasuda	Dosage Form	Tablet and chewable tablet
		Dosing Regimen	Based upon dose escalation to 100 mg/day to 400 mg/day-group dependent
Date of Submission	February 4, 2005	Route of Administration	Oral
Estimated Due Date of OCPB Review	October 19, 2005	Sponsor	Glaxo Smith Kline
PDUFA Due Date	December 7, 2005	Priority Classification	1S
Division Due Date	November 5, 2005		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	x			Revisions to current label and addition of adjunct therapy (b) (4)
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	x		LAM40097	Seeking an indication for adjunct therapy in adults and children(2-12yrs) but only lamotrigine levels were measured. The other information is a rationale for (b) (4)
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				

PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

Filability and QBR comments		
	"X" if yes	**Comments**
Application fileable ?	**Yes**	
Comments sent to firm ?		
QBR questions (key issues to be considered)	**1.** (b) (4) **2.**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA HFD-850 (Electronic Entry or Lee), HFD-120 (CSO), HFD-860 (Jackson, Mehta,Yasuda, Rahman), CDR (Biopharm-CDR)

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/s/

Andre Jackson
3/30/05 07:31:59 AM
BIOPHARMACEUTICS

Sally Yasuda
4/8/05 08:48:42 AM
BIOPHARMACEUTICS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-241/S-027/(b) (4)
NDA 20-764/ (b) (4) S-022

SmithKlineBeecham
d/b/a GlaxoSmithKline
Attn: Elizabeth McConnell, Pharm.D.
Associate Director, Regulatory Affairs, Neurology
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Dr. McConnell:

We have received your new drug applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product	Reference Number	Indication
Lamictal (lamotrigine) Tablets	NDA 20-241/S-027	Adjunctive treatment of primary generalized tonic-clonic seizures in adults and pediatric patients
Lamictal (lamotrigine) Chewable Dispersible Tablets	NDA 20-764/S-020	
(b) (4)		

Review Priority Classification: Standard (S)

Date of Application: February 4, 2005

Date of Receipt: February 7, 2005

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 8, 2005 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be December 7, 2005.

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 note that you have submitted pediatric studies with this application. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room, 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological, HFD-120
Attention: Document Room 4008
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, call Courtney Calder, Pharm.D., Regulatory Project Manager, at (301) 594-5315.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Division of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Katz
3/15/05 03:41:55 PM