

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

Approval Package for:

APPLICATION NUMBER:

20-241/S-011

20-764/S-005

Trade Name: Lamictal Tablets and Lamictal
Chewable Dispersible Tablets

Generic Name: lamotrigine

Sponsor: Glaxo Wellcome Inc.

Approval Date: May 25, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-241/S-011

20-764/S-005

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter(s)	X
Tentative Approval Letter(s)	
Final Printed Labeling	X
CSO Labeling Review(s)	
Medical Officer Review(s)	X
Chemistry Review(s)	X
Microbiology Review(s)	
Bioequivalence Review(s)	
Administrative Document(s)	X
Correspondence	X

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-241/S-011

20-764/S-005

APPROVAL LETTER



NDA 20-241/S-011
NDA 20-764/S-005

Glaxo Wellcome Inc.
Attention: Elizabeth A. McConnell, Pharm.D.
Project Director, Regulatory Affairs
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709-3398

Dear Dr. McConnell:

Please refer to your supplemental new drug applications dated August 20, 1999, received November 4, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lamictal Tablets and Lamictal Chewable Dispersible Tablets.

We acknowledge receipt of your submissions dated October 21, 1999, November 1, 1999, August 28, 2000, and November 27, 2000. Your submission of November 27, 2000 constituted a complete response to our August 24, 2000 action letter.

These supplemental new drug applications provide clinical data in support of a labeling revision to update the Geriatric Use subsection of the Lamictal package insert. Specifically, these applications originally proposed to include standard language contained in paragraph (B) under 21 CFR 201.57(f)(10)(ii), which basically states that no differences in safety or effectiveness have been observed between elderly and younger subjects. Currently, as amended, these applications propose revised standard language (as recommended in the Agency's August 24, 2000 action letter) contained in paragraph (A) under 21 CFR 201.57(f)(10)(ii), which basically states that dose selection in the elderly should be cautious.

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

The final printed labeling (FPL) must be identical to the enclosed draft labeling text (dated May 25, 2001), and must be formatted in accordance with the requirements of 21 CFR 201.66. Marketing the products with FPL that is not identical to the approved labeling text and "Drug Facts" format may render the products misbranded and unapproved new drugs.

Please submit the copies of final printed labeling (FPL) electronically to each application according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*

NDA 20-241/S-011

NDA 20-764/S-005

Page 2

(January 1999). 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. Please individually mount ten of the copies on heavyweight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplements NDA 20-241/S-011 and 20-764/S-005." Approval of these submissions by FDA is not required before the labeling is used.

In addition, we note that your November 27, 2000 response to our August 24, 2000 action letter did not include new data or new analyses. We remind you that our action letter requested that you further evaluate any potential differences between the pharmacokinetics in the elderly and younger adults. Specifically, based on our initial review of these applications, there is a suggestion of a 33% difference in clearance between elderly and young adults in one comparison of the 2 groups, the UK study in 12 elderly and 12 younger adults. While the clearance in these 12 elderly patients is comparable to the clearance in an extended sample of young adults, we believe the discrepancy in the UK study requires explanation. Therefore, we are asking you, again, to revisit this issue and explore explanations for these results. As we stated in our action, we would be happy to discuss this with you, but at the least we ask you to submit a discussion of these discrepant results.

Lastly, please submit three copies of the introductory promotional materials that you propose to use for these products. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package inserts directly to:

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

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

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

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

NDA 20-241/S-011

NDA 20-764/S-005

Page 3

If you have any questions, call Jacqueline H. Ware, Pharm.D., Regulatory Management Officer, at (301) 594-5533.

Sincerely,

{See appended electronic signature page}

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

APPEARS THIS WAY
ON ORIGINAL

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-241/S-011

20-764/S-005

FINAL PRINTED LABELING

FDA Approved Labeling Text for NDA 20-764/S-005 and NDA 20-241/S-011 dated 5/25/01

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

LAMICTAL[®]

PRODUCT INFORMATION

(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 1% (1/100) IN PEDIATRIC PATIENTS (AGE <16 YEARS) AND 0.3% (3/1000) IN ADULTS. IN WORLDWIDE POSTMARKETING EXPERIENCE, RARE CASES OF TOXIC EPIDERMAL NECROLYSIS AND/OR RASH-RELATED DEATH HAVE BEEN REPORTED, BUT THEIR NUMBERS ARE TOO FEW TO PERMIT A PRECISE ESTIMATE OF THE RATE.

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

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 VALPROIC ACID (VPA), 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.

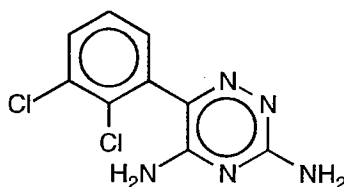
NEARLY ALL CASES OF LIFE-THREATENING RASHES ASSOCIATED WITH LAMICTAL HAVE OCCURRED WITHIN 2 TO 8 WEEKS OF TREATMENT INITIATION. HOWEVER, ISOLATED CASES HAVE BEEN REPORTED AFTER PROLONGED TREATMENT (e.g., 6 MONTHS). ACCORDINGLY, DURATION OF THERAPY CANNOT BE RELIED UPON AS A MEANS TO PREDICT THE POTENTIAL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

ALTHOUGH BENIGN RASHES ALSO OCCUR WITH LAMICTAL, IT IS NOT POSSIBLE TO

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

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. 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

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

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).

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-HT₃ receptor (IC₅₀ = 18 μM). It does not exhibit high affinity binding (IC₅₀>100 μM) to the following neurotransmitter receptors: adenosine A₁ and A₂; adrenergic α₁, α₂, and β; dopamine D₁ and D₂; γ-aminobutyric acid (GABA) A and B; histamine H₁; kappa opioid; muscarinic acetylcholine; and serotonin 5-HT₂. Studies have failed to detect an effect of lamotrigine on dihydropyridine-sensitive calcium channels. It had weak effects at sigma opioid receptors (IC₅₀ = 145 μM). Lamotrigine did not inhibit the uptake of norepinephrine, dopamine, serotonin, or aspartic acid (IC₅₀>100 μM).

Effect of Lamotrigine on N-Methyl d-Aspartate (NMDA)-Mediated Activity: Lamotrigine did not inhibit 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 IC₅₀ 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 folic 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

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

lamotrigine dose) have been found in human urine (see Drug Disposition below). 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.

**APPEARS THIS WAY
ON ORIGINAL.**

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00

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

**Table 1: Mean* Pharmacokinetic Parameters
in Adult Patients With Epilepsy or Healthy Volunteers**

Adult Study Population	Number of Subjects	t _{max} : Time of Maximum Plasma Concentration (h)	t _{1/2} : Elimination Half-life (h)	Cl/F: Apparent Plasma Clearance (mL/min/kg)
Patients taking enzyme-inducing antiepileptic drugs (EIAEDs) [†] :				
Single-dose LAMICTAL	24	2.3 (0.5-5.0)	14.4 (6.4-30.4)	1.10 (0.51-2.22)
Multiple-dose LAMICTAL	17	2.0 (0.75-5.93)	12.6 (7.5-23.1)	1.21 (0.66-1.82)
Patients taking EIAEDs + VPA:				
Single-dose LAMICTAL	25	3.8 (1.0-10.0)	27.2 (11.2-51.6)	0.53 (0.27-1.04)
Patients taking VPA only:				
Single-dose LAMICTAL	4	4.8 (1.8-8.4)	58.8 (30.5-88.8)	0.28 (0.16-0.40)
Healthy volunteers taking VPA:				
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)
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)

*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.

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

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

The apparent clearance of lamotrigine is affected by the coadministration of AEDs.

Lamotrigine is eliminated more rapidly in patients who have been taking hepatic EIAEDs, including carbamazepine, phenytoin, phenobarbital, and primidone. Most clinical experience is derived from this population.

VPA, however, actually decreases the apparent clearance of lamotrigine (i.e., more than doubles the elimination half-life of lamotrigine), whether given with or without EIAEDs.

Accordingly, if lamotrigine is to be administered to a patient receiving VPA, lamotrigine must be given at a reduced dosage, less than half the dose used in patients not receiving VPA (see DOSAGE AND ADMINISTRATION 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 four to six 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 VPA. 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 ¹⁴C-lamotrigine (15 μCi) to six healthy volunteers, 94% was recovered in the urine and 2% was recovered in the feces. The radioactivity in the urine consisted of unchanged lamotrigine (10%), the 2-N-glucuronide (76%), a 5-N-glucuronide (10%), a 2-N-methyl metabolite (0.14%), and other unidentified minor metabolites (4%).

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

Following multiple administrations (150 mg twice daily) to normal volunteers taking no other medications, lamotrigine induced its own metabolism, resulting in a 25% decrease in T_½ and a 37%

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

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 EIAEDs.

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 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 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 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 by hemodialysis during a 4-hour session.

Hepatic Disease: The pharmacokinetic parameters of lamotrigine in patients with impaired liver function have not been studied.

Age: Pediatric Patients: The pharmacokinetics of LAMICTAL following a single 2-mg/kg dose were evaluated in two studies of pediatric patients with epilepsy (n = 25 for patients aged 10 months to 5.3 years and n = 19 for patients aged 5 to 11 years). All patients were receiving concomitant therapy with other AEDs. Lamotrigine pharmacokinetic parameters for pediatric patients are summarized in Table 2.

As with adults, the elimination of lamotrigine in pediatric patients was similarly affected by concomitant AEDs. Weight normalized oral clearance (Cl/F) was higher (onefold to threefold) in infants and children (age 10 months to 11 years) than in the adolescents and adults, while adolescents and adults had similar mean values of Cl/F.

APPEARS THIS WAY
ON ORIGINAL

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

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 EIAEDs	10	3.0 (1.0-5.9)	7.7 (5.7-11.4)	3.62 (2.44-5.28)
Patients taking AEDs with no known effect on drug-metabolizing enzymes	7	5.2 (2.9-6.1)	19.0 (12.9-27.1)	1.2 (0.75-2.42)
Patients taking VPA 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 EIAEDs	7	1.6 (1.0-3.0)	7.0 (3.8-9.8)	2.54 (1.35-5.58)
Patients taking EIAEDs plus VPA	8	3.3 (1.0-6.4)	19.1 (7.0-31.2)	0.89 (0.39-1.93)
Patients taking VPA 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 EIAEDs	11	†	†	1.3
Patients taking EIAEDs plus VPA	8	†	†	0.5
Patients taking VPA only	4	†	†	0.3

*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.

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

CLINICAL STUDIES: The results of controlled clinical trials established the efficacy of LAMICTAL as monotherapy in adults with partial onset seizures already receiving treatment with a single

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

enzyme-inducing antiepileptic drug (EIAED), as adjunctive therapy in adults 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 a Single EIAED: 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 four simple partial, complex partial, and/or secondarily generalized seizures during each of two consecutive 4-week periods while receiving carbamazepine or phenytoin monotherapy during baseline. LAMICTAL (target dose of 500 mg/day) or VPA (1000 mg/day) was added to either carbamazepine or phenytoin monotherapy over a 4-week period. Patients were then converted to monotherapy with LAMICTAL or VPA 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 VPA 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: The effectiveness of LAMICTAL as adjunctive therapy (added to other AEDs) was established in three 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 three 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,

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL[®] (lamotrigine) Tablets
LAMICTAL[®] (lamotrigine) Chewable Dispersible Tablets

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 two other anticonvulsants and VPA 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 two other anticonvulsants and VPA 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 two other anticonvulsants. Thirteen patients were on concomitant VPA; 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 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 three drugs. Patients were dosed on a fixed-dose regimen based on body weight and VPA use. Target doses were designed to approximate 5 mg/kg per day for patients taking VPA (maximum dose, 200 mg/day) and 15 mg/kg per day for patients not taking VPA (maximum dose, 400 mg/day). The primary efficacy endpoint was median reduction 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

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL[®] (lamotrigine) Tablets
LAMICTAL[®] (lamotrigine) Chewable Dispersible Tablets

tonic-clonic seizures (36% reduction versus 10% increase for LAMICTAL and placebo, respectively).

INDICATIONS AND USAGE:

Adjunctive Use: LAMICTAL is indicated as adjunctive therapy in adults with partial seizures and as adjunctive therapy in the generalized seizures of Lennox-Gastaut syndrome in pediatric and adult patients.

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

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

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

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 was approximately 1.1% (14/1233). When these 14 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 were no deaths or permanent sequelae in these patients. Additionally, there have been rare cases of toxic epidermal necrolysis with and without permanent sequelae and/or death in US and foreign postmarketing experience. It bears emphasis, accordingly, that LAMICTAL is only approved for use in those patients below the age of 16 who have seizures associated with the Lennox-Gastaut syndrome (see INDICATIONS).

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

Because foreign postmarketing reports suggested that the rate of serious rash was greater with concomitant VPA use and because metabolism of LAMICTAL is inhibited by VPA, resulting in increased LAMICTAL plasma levels, the drug development database was examined for concomitant VPA use. In pediatric patients who used VPA concomitantly, 1.1% (5/443) experienced a serious rash compared to 1% (6/628) patients not taking VPA. Although the numbers are small, 1.7% (5/294) patients taking either VPA alone or VPA + non-EIAEDs experienced a serious rash compared to 0% (0/149) patients taking VPA + EIAEDs.

Adult Population: Serious rash associated with hospitalization and discontinuation of LAMICTAL occurred in 0.3% (11/3348) of patients who received LAMICTAL in premarketing clinical trials. 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 VPA in a multidrug regimen increases the risk of serious, potentially life-threatening rash in adults. Specifically, of 584 patients administered LAMICTAL with VPA in clinical trials, 6 (1%) were hospitalized in association with rash; in contrast, 4 (0.16%) of 2398 clinical trial patients and volunteers administered LAMICTAL in the absence of VPA were hospitalized.

Other examples of serious and potentially life-threatening rash that did not lead to hospitalization also occurred in premarketing development. Among these, one 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 dysfunction such as 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: Fatalities associated with multiorgan failure and various degrees of hepatic failure have been reported in 2/3796 adult patients and 3/1136 pediatric patients who received LAMICTAL during premarketing clinical trials. Rare fatalities from multiorgan failure have

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

also been reported in compassionate plea and postmarketing use. All of these cases occurred in association with other serious medical events (e.g., status epilepticus, overwhelming sepsis), making it impossible to identify the initiating cause.

Additionally, three 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 two patients. Both pediatric patients were receiving concomitant therapy with VPA, while the adult patient was being treated with carbamazepine and clonazepam. All patients subsequently recovered with supportive care after treatment with LAMICTAL was discontinued.

Pure Red Cell Aplasia (PRCA): A case of PRCA was reported in a 32-year-old male with a history of β -thalassemia. The patient had a microcytic anemia (hemoglobin 11 g/dL) that was stable while the patient received carbamazepine but became more severe in the 3 months after LAMICTAL was added. A bone marrow aspirate revealed markedly decreased erythropoiesis but normal granulopoiesis and thrombopoiesis. Erythropoiesis resumed after discontinuation of LAMICTAL and transfusions of packed red cells. Although PRCA is known to occur in patients with hemoglobinopathies, it is not known if β -thalassemia is a specific risk factor for the development of PRCA.

Withdrawal Seizures: As a rule, AEDs should not be abruptly discontinued because of the possibility of increasing seizure frequency. 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:

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 VPA, 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 clinical trials, approximately 10% of all 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

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

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.**

Sudden Unexplained Death in Epilepsy (SUDEP): During the premarketing development of LAMICTAL, 20 sudden and unexplained deaths were recorded among a cohort of 4700 patients with epilepsy (5747 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 2343 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.

Addition of LAMICTAL to a Multidrug Regimen That Includes VPA (Dosage Reduction):

Because VPA reduces the clearance of lamotrigine, the dosage of lamotrigine in the presence of VPA 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

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

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 no 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.

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 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.

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 AEDs being taken concomitantly (see Table 3), monitoring of the plasma levels of LAMICTAL and concomitant AEDs may be indicated, particularly during dosage adjustments. In general, clinical judgment should be exercised regarding monitoring of plasma levels of LAMICTAL and other anti-seizure drugs and whether or not dosage adjustments are necessary.

Drug Interactions: Antiepileptic Drugs: The use of AEDs in combination is complicated by the

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

potential for pharmacokinetic interactions.

The interaction of lamotrigine with phenytoin, carbamazepine, and VPA has been studied. The net effects of these various AED combinations on individual AED plasma concentrations are summarized in Table 3.

Table 3: Summary of AED Interactions With LAMICTAL

AED	AED Plasma Concentration With Adjunctive LAMICTAL*	Lamotrigine Plasma Concentration With Adjunctive AEDs†
Phenytoin (PHT)	↔	↓
Carbamazepine (CBZ)	↔	↓
CBZ epoxide‡	?	
Valproic acid (VPA)	↓	↑
VPA + PHT and/or CBZ	NE	↔

* 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.

NE = Not evaluated.

Specific Effects of Lamotrigine on the Pharmacokinetics of Other AED Products:

LAMICTAL Added to Phenytoin: LAMICTAL has no appreciable effect on steady-state phenytoin plasma concentration.

LAMICTAL Added to 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 EIAEDs with LAMICTAL (see ADVERSE REACTIONS). The mechanism of this interaction is unclear. The effect of lamotrigine on plasma concentrations of carbamazepine-epoxide is unclear. In a small subset of patients (n = 7) studied in a placebo-controlled trial, lamotrigine had no effect on carbamazepine-epoxide plasma concentrations, but in a small, uncontrolled study (n = 9), carbamazepine-epoxide levels were seen to increase.

LAMICTAL Added to VPA: When LAMICTAL was administered to 18 healthy volunteers receiving VPA in a pharmacokinetic study, the trough steady-state VPA concentrations in plasma 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 plasma VPA concentrations in either

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

adult or pediatric patients in controlled clinical trials.

Specific Effects of Other AED Products on the Pharmacokinetics of Lamotrigine: Phenytoin Added to LAMICTAL: The addition of phenytoin decreases lamotrigine steady-state concentrations by approximately 45% to 54% depending upon the total daily dose of phenytoin (i.e., from 100 to 400 mg).

Carbamazepine Added to LAMICTAL: The addition of carbamazepine decreases lamotrigine steady-state concentrations by approximately 40%.

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

VPA Added to LAMICTAL: The addition of VPA increases lamotrigine steady-state concentrations in normal volunteers by slightly more than twofold.

Interactions With Drug Products Other Than AEDs: Folate Inhibitors: Lamotrigine is an inhibitor of dihydrofolate reductase. Prescribers should be aware of this action when prescribing other medications that inhibit folate metabolism.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenicity was seen in one mouse study or two 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/m² and 60 to 90 mg/m², 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 two gene mutation assays (the Ames test and the in vitro mammalian mouse lymphoma assay). In two 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/m² basis. The effect of lamotrigine on human fertility is unknown.

Pregnancy: 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/m² 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

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

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/m² 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/m² basis.

When pregnant rats were orally dosed at 0.1, 0.14, or 0.3 times the highest human maintenance dose (on a mg/m² 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 three drug-treated groups with the highest number in the high-dose group. Postnatal death was also seen, but only in the two 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.

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: In pediatric patients, LAMICTAL is only indicated as adjunctive therapy for the generalized seizures of Lennox-Gastaut syndrome. Safety and effectiveness for other uses in patients below the age of 16 years have not been established (see BOX WARNING).

Geriatric Use: Clinical studies of LAMICTAL did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

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).

Most Common Adverse Events in All Clinical Studies: *Adjunctive Therapy in Adults:* The most commonly observed ($\geq 5\%$) 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 EIAEDs with LAMICTAL. Clinical data suggest a higher incidence of rash, including serious rash, in patients receiving concomitant VPA than in patients not receiving VPA (see WARNINGS).

Approximately 11% of the 3378 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: The most commonly observed ($\geq 5\%$) 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 ($\geq 5\%$) 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

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

events most commonly associated with discontinuation were rash (4.5%), headache (3.1%), and asthenia (2.4%).

Adjunctive Therapy in Pediatric Patients With Lennox-Gastaut Syndrome: The most commonly observed ($\geq 5\%$) adverse experiences seen in association with the use of LAMICTAL as adjunctive treatment in pediatric patients with Lennox-Gastaut syndrome and not seen at an equivalent rate in the control group were pharyngitis, infection, rash, vomiting, bronchitis, accidental injury, constipation, and flu syndrome.

In 169 patients with Lennox-Gastaut syndrome (26 patients were between the ages of 16 and 25), 3.8% of patients on LAMICTAL and 7.8% 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 10% of the 1136 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 (3.9%), reaction aggravated (1.7%), and ataxia (0.9%).

Incidence in Controlled Clinical Studies: 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: 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.

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

Table 4: Treatment-Emergent Adverse Event Incidence in Placebo-Controlled Adjunctive Trials*
(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

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

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 one to three concomitant EIAEDs 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).

**APPEARS THIS WAY
ON ORIGINAL**

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

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

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

*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 2% 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.

APPEARS THIS WAY
ON ORIGINAL

LAMICTAL® (lamotrigine) Tablets

LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

Table 6: Treatment-Emergent Adverse Event Incidence

in Adults in a Controlled Monotherapy Trial*

(Events in at least 2% of patients treated with LAMICTAL

and numerically more frequent than in the valproate [VPA] group.)

Body System/ Adverse Experience [†]	Percent of Patients Receiving LAMICTAL Monotherapy [‡] (n = 43)	Percent of Patients Receiving Low-Dose VPA [§] Monotherapy (n = 44)
Body as a whole		
Pain	5	0
Infection	5	2
Chest pain	5	2
Asthenia	2	0
Fever	2	0
Digestive		
Vomiting	9	0
Dyspepsia	7	2
Nausea	7	2
Anorexia	2	0
Dry mouth	2	0
Rectal hemorrhage	2	0
Peptic ulcer	2	0
Metabolic and nutritional		
Weight decrease	5	2
Peripheral edema	2	0
Nervous		
Coordination abnormality	7	0
Dizziness	7	0
Anxiety	5	0
Insomnia	5	2
Amnesia	2	0
Ataxia	2	0
Depression	2	0
Hypesthesia	2	0
Libido increase	2	0
Decreased reflexes	2	0

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00

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

Increased reflexes	2	0
Nystagmus	2	0
Irritability	2	0
Suicidal ideation	2	0
Respiratory		
Rhinitis	7	2
Epistaxis	2	0
Bronchitis	2	0
Dyspnea	2	0
Skin and appendages		
Contact dermatitis	2	0
Dry skin	2	0
Sweating	2	0
Special senses		
Vision abnormality	2	0
Urogenital (female patients only)	(n = 21)	(n = 28)
Dysmenorrhea	5	0

* Patients in these studies were converted to LAMICTAL or VPA 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 2% of patients are included.

‡ Up to 500 mg/day.

§ 1000 mg/day.

Incidence in a Controlled Adjunctive Trial in Adult and Pediatric Patients With

Lennox-Gastaut Syndrome: Table 7 lists adverse events that occurred in at least 2% of 79 adult and pediatric patients who received LAMICTAL up to 15 mg/kg per day or a maximum of 400 mg per day. Reported adverse events were classified using COSTART terminology.

**APPEARS THIS WAY
ON ORIGINAL**

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

**Table 7: Treatment-Emergent Adverse Event Incidence in Placebo-Controlled
Adjunctive Trial in Adult and Pediatric Patients With Lennox-Gastaut Syndrome
(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 = 79)	Percent of Patients Receiving Placebo (n = 90)
Body as a whole		
Infection	13	8
Accidental injury	9	7
Flu syndrome	5	0
Asthenia	3	1
Abdominal pain	3	0
Cardiovascular		
Hemorrhage	3	0
Digestive		
Vomiting	9	7
Constipation	5	2
Diarrhea	4	2
Nausea	4	1
Anorexia	3	1
Nervous system		
Ataxia	4	1
Convulsions	4	1
Tremor	3	0
Respiratory		
Pharyngitis	14	10
Bronchitis	9	7
Pneumonia	3	0
Skin		
Rash	9	7
Eczema	4	0
Urogenital		

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

Urinary tract infection	3	0
Balanitis	2	0
Penis disorder	2	0

Other Adverse Events Observed During All Clinical Trials For Adult and Pediatric Patients:

LAMICTAL has been administered to 3923 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 3923 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 table, 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 1/1000 patients; *rare* adverse events are those occurring in fewer than 1/1000 patients.

Body as a Whole: Frequent: Pain. **Infrequent:** Accidental injury, allergic reaction, back pain, chills, face edema, halitosis, infection, and malaise. **Rare:** Abdomen enlarged, abscess, photosensitivity, and suicide attempt.

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

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

Digestive System: Infrequent: Dry mouth, dysphagia, gingivitis, glossitis, gum hyperplasia, increased appetite, increased salivation, liver function tests abnormal, mouth ulceration, stomatitis, thirst, and tooth disorder. **Rare:** Eructation, gastritis, gastrointestinal hemorrhage, gum hemorrhage, hematemesis, hemorrhagic colitis, hepatitis, melena, stomach ulcer, and tongue edema.

Endocrine System: Rare: Goiter and hypothyroidism.

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

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

Metabolic and Nutritional Disorders: Infrequent: Peripheral edema, weight gain, and weight loss. **Rare:** Alcohol intolerance, alkaline phosphatase increase, bilirubinemia, general edema, and hyperglycemia.

Musculoskeletal System: Infrequent: Joint disorder, myasthenia, and twitching. **Rare:** Arthritis, bursitis, leg cramps, pathological fracture, and tendinous contracture.

Nervous System: Frequent: Amnesia, confusion, hostility, memory decrease, nervousness, nystagmus, thinking abnormality, and vertigo. **Infrequent:** Abnormal dreams, abnormal gait, agitation, akathisia, apathy, aphasia, CNS depression, depersonalization, dysarthria, dyskinesia, dysphoria, emotional lability, euphoria, faintness, grand mal convulsions, hallucinations, hyperkinesia, hypertonia, hypesthesia, libido increased, mind racing, muscle spasm, myoclonus, panic attack, paranoid reaction, personality disorder, psychosis, sleep disorder, and stupor. **Rare:** Cerebrovascular accident, cerebellar syndrome, cerebral sinus thrombosis, choreoathetosis, CNS stimulation, delirium, delusions, dystonia, hemiplegia, hyperalgesia, hyperesthesia, hypoesthesia, hypokinesia, hypomania, hypotonia, libido decreased, manic depression reaction, movement disorder, neuralgia, neurosis, paralysis, and suicidal ideation.

Respiratory System: Infrequent: Dyspnea, epistaxis, and hyperventilation. **Rare:** Bronchospasm, hiccup, and sinusitis.

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

Urogenital System: Infrequent: Female lactation, hematuria, polyuria, urinary frequency, urinary incontinence, urinary retention, and vaginal moniliasis. **Rare:** Abnormal ejaculation, acute kidney failure, breast abscess, breast neoplasm, breast pain, creatinine increase, cystitis, dysuria, epididymitis, impotence, kidney failure, kidney pain, menorrhagia, and urine abnormality.

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.

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00

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

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: Experience with single or daily doses ≥ 700 mg is limited. During the clinical development of LAMICTAL, the highest known overdoses were in two women who each ingested doses ≥ 4000 mg. The plasma concentration of lamotrigine in one woman was 52 mcg/mL 4 hours after the ingestion (a value more than 10 times greater than that seen in clinical trials). She became comatose and remained comatose for 8 to 12 hours; no electrocardiographic abnormalities were detected. The other patient had dizziness, headache, and somnolence. Both women recovered without sequelae.

Among patients ≤ 16 years of age, the two highest known single doses of LAMICTAL have been 3000 mg by a 14-year-old female and approximately 1000 mg by a 4-year-old male. The 14-year-old female was taking LAMICTAL; after the dose, she lost consciousness and was admitted to the hospital for supportive therapy, where she recovered fully (time to recovery not reported). The 4-year-old male was drowsy and agitated when found, and progressed to coma. He was given supportive therapy, and his condition improved rapidly with full recovery in 3 days.

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 six 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 overdose of LAMICTAL.

DOSAGE AND ADMINISTRATION:

Adjunctive Use: LAMICTAL is indicated as adjunctive therapy in adults with partial seizures and as adjunctive therapy in the generalized seizures of Lennox-Gastaut syndrome in pediatric and adult patients.

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

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL[®] (lamotrigine) Tablets
LAMICTAL[®] (lamotrigine) Chewable Dispersible Tablets

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

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

General Dosing Considerations: 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 valproic acid (VPA), 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.

Adjunctive Therapy With LAMICTAL: 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 whether or not the patient is receiving VPA (Tables 8 and 9 for patients 2 to 12 years of age, Tables 10 and 11 for patients greater than 12 years of age). In addition, the section provides a discussion of dosing for those patients receiving concomitant AEDs that have not been systematically evaluated in combination with LAMICTAL.

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

Patients 2 to 12 Years of Age: Recommended dosing guidelines for LAMICTAL added to an antiepileptic drug (AED) regimen containing VPA are summarized in Table 8. Recommended dosing guidelines for LAMICTAL added to EIAEDs are summarized in Table 9.

LAMICTAL Added to AEDs Other Than EIAEDs and VPA: The effect of AEDs other than EIAEDs and VPA on the metabolism of LAMICTAL is not currently known. Therefore, no specific dosing guidelines can be provided in that situation. Conservative starting doses and dose escalations (as with concomitant VPA) would be prudent; maintenance dosing would be expected to fall between the maintenance dose with VPA and the maintenance dose without VPA, but with an EIAED.

Note that the starting doses and dose escalations listed below 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. It is likely that patients aged 2 to 6 years will require a maintenance dose at the higher end of the maintenance dose range.

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

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 LAMICTAL Chewable Dispersible Tablet available sizes).

**APPEARS THIS WAY
ON ORIGINAL**

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

**Table 8: LAMICTAL Added to an AED Regimen Containing VPA
in Patients 2 to 12 Years of Age**

Weeks 1 and 2		0.15 mg/kg/day in one or two divided doses, rounded down to the nearest whole tablet. Only whole tablets should be used for dosing.	
Weeks 3 and 4		0.3 mg/kg/day in one or two divided doses, rounded down to the nearest whole tablet.	
Weight based dosing can be achieved by using the following guide:			
If the patient's weight is		Give this daily dose, using the most appropriate combination of Lamictal 2 mg and 5 mg tablets	
Greater than	And less than	Weeks 1 and 2	Weeks 3 and 4
6.7 kg	14 kg	2 mg every <i>other</i> day	2 mg every day
14.1 kg	27 kg	2 mg every day	4 mg every day
27.1 kg	34 kg	4 mg every day	8 mg every day
34.1 kg	40 kg	5 mg every day	10 mg every day
Usual maintenance dose: 1 to 5 mg/kg/day (maximum 200 mg/day in one or two divided doses). To achieve the usual maintenance dose, subsequent doses should be increased every 1 to 2 weeks as follows: calculate 0.3 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily dose.			

Table 9: LAMICTAL Added to EIAEDs (Without VPA) in Patients 2 to 12 Years of Age

Weeks 1 and 2		0.6 mg/kg/day in two divided doses, rounded down to the nearest whole tablet.	
Weeks 3 and 4		1.2 mg/kg/day in two divided doses, rounded down to the nearest whole tablet.	
Usual maintenance dose: 5 to 15 mg/kg/day (maximum 400 mg/day in two divided doses). To achieve the usual maintenance dose, subsequent doses should be increased every 1 to 2 weeks as follows: calculate 1.2 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily dose.			

Patients Over 12 Years of Age: Recommended dosing guidelines for LAMICTAL added to VPA are summarized in Table 10. Recommended dosing guidelines for LAMICTAL added to EIAEDs are summarized in Table 11.

LAMICTAL Added to AEDs Other Than EIAEDs and VPA: The effect of AEDs other than EIAEDs and VPA on the metabolism of LAMICTAL is not currently known. Therefore, no specific

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

dosing guidelines can be provided in that situation. Conservative starting doses and dose escalations (as with concomitant VPA) would be prudent; maintenance dosing would be expected to fall between the maintenance dose with VPA and the maintenance dose without VPA, but with an EIAED.

**Table 10: LAMICTAL Added to an AED Regimen Containing VPA
in Patients Over 12 Years of Age**

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

Table 11: LAMICTAL Added to EIAEDs (Without VPA) in Patients Over 12 Years of Age

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

Conversion From a Single EIAED to Monotherapy With LAMICTAL in Patients ≥16 Years of Age: 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 conversion regimen involves two steps. In the first, LAMICTAL is titrated to the targeted dose while maintaining the dose of the EIAED at a fixed level; in the second step, the EIAED is gradually withdrawn over a period of 4 weeks.

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

LAMICTAL should be added to an EIAED to achieve a dose of 500 mg/day according to the guidelines in Table 11 above. The regimen for the withdrawal of the concomitant EIAED is based on experience gained in the controlled monotherapy clinical trial. In that trial, the concomitant EIAED was withdrawn by 20% decrements each week over a 4-week period.

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

Usual Maintenance Dose: The usual maintenance doses identified in the tables above are derived from dosing regimens employed in the placebo-controlled adjunctive studies in which the efficacy of

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

LAMICTAL was established. In patients receiving multidrug regimens employing EIAEDs **without VPA**, maintenance doses of adjunctive LAMICTAL as high as 700 mg/day have been used. In patients receiving **VPA alone**, maintenance doses of adjunctive LAMICTAL as high as 200 mg/day have been used. The advantage of using doses above those recommended in the tables above has not been established in controlled trials.

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.

Discontinuation Strategy: 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 an EIAED should prolong the half-life of lamotrigine; discontinuing VPA should shorten the half-life of lamotrigine.

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

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"

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00

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

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 GLAXO WELLCOME, INC. 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.

**APPEARS THIS WAY
ON ORIGINAL**





FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00

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




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

Information for the Patient

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
--	---	--

NOTE: The pictures above 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. Before taking your medicine, it is important to compare the tablets you receive from your doctor or pharmacist with these pictures to make sure you have received the correct medicine.

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.

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

1. The Purpose of Your Medicine:

Lamotrigine is intended to be used either alone or in combination with other medicines to treat seizures in people age 16 years or older and/or only those patients below the age of 16 years who have seizures associated with the Lennox-Gastaut syndrome. When taking lamotrigine, it is important to follow your doctor's instructions.

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. The most common side effects with LAMICTAL are dizziness, headache, blurred or double vision, lack of coordination, sleepiness, nausea, vomiting, and rash.
- 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 valproic acid (DEPAKENE® or DEPAKOTE®), 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 Breast-feeding:

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. 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.
- If you miss a dose of LAMICTAL, do not double your next dose.

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00

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

- Do NOT stop taking LAMICTAL or any of your other seizure 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.
- Tell your doctor if your seizures get worse or if you have any new types of seizures.
- Always tell your doctor and pharmacist if you are taking or plan to take any other prescription or over-the-counter medicines.

6. 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.

7. 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. 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.

GlaxoWellcome

Glaxo Wellcome Inc.

Research Triangle Park, NC 27709

DEPAKENE and DEPAKOTE are registered trademarks of Abbott Laboratories.

US Patent No. 4,602,017 and 5,698,226

©Copyright 1998, 1999, 2000, Glaxo Wellcome Inc. All rights reserved.

November 2000





RL-

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00
LAMICTAL® (lamotrigine) Tablets
LAMICTAL® (lamotrigine) Chewable Dispersible Tablets




PHARMACIST--DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

Information for the Patient

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
---	--	---

NOTE: The pictures above 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. Before taking your medicine, it is important to compare the tablets you receive from your doctor or pharmacist with these pictures to make sure you have received the correct medicine.

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

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

you and your doctor should make together.

1. The Purpose of Your Medicine:

Lamotrigine is intended to be used either alone or in combination with other medicines to treat seizures in people age 16 years or older and/or only those patients below the age of 16 years who have seizures associated with the Lennox-Gastaut syndrome. When taking lamotrigine, it is important to follow your doctor's instructions.

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. The most common side effects with LAMICTAL are dizziness, headache, blurred or double vision, lack of coordination, sleepiness, nausea, vomiting, and rash.
- 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 valproic acid (DEPAKENE® or DEPAKOTE®), 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 Breast-feeding:

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. 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.

FDA Approved Labeling Text for NDA 20-764/S-006 and NDA 20-241/S-014 dated 9/8/00

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

- If you miss a dose of lamotrigine, do not double your next dose.
- Do NOT stop taking LAMICTAL or any of your other seizure 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.
- Tell your doctor if your seizures get worse or if you have any new types of seizures.
- Always tell your doctor and pharmacist if you are taking or plan to take any other prescription or over-the-counter medicines.

6. 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.

7. 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. 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.

GlaxoWellcome

Glaxo Wellcome Inc.

Research Triangle Park, NC 27709

DEPAKENE and DEPAKOTE are registered trademarks of Abbott Laboratories.

US Patent No. 4,602,017 and 5,698,226

©Copyright 1998, 1999, 2000, Glaxo Wellcome Inc. All rights reserved.

November 2000

RL-

**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
5/25/01 01:20:05 PM

APPEARS THIS WAY
ON ORIGINAL

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-241/S-011

20-764/S-005

**MEDICAL OFFICER
REVIEW(S)**

MEMORANDUM

DATE: May 21, 2001

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

SUBJECT: NDA 20-241/S-011, Lamictal Geriatric Supplement
NDA 20-764/S-005, Lamictal Geriatric Supplement
Response to Not Approvable Letter

Introduction

On August 24, 2000, Glaxo Wellcome was sent a Not Approvable letter for the above supplements (which provided for geriatric labeling changes). In that letter, the sponsor was informed that the relevant experience in geriatric patients remained extremely small and would allow for only a general statement about potential risks in elderly patients. The sponsor was also asked to investigate potential age-related differences in pharmacokinetics.

Current Submission

The current response does not provide any new safety or pharmacokinetic data.

In this response, the sponsor has agreed to a general statement of potential risks in elderly patients.

Current labeling states there are no age-related PK differences in elderly. The Clin Pharm section currently states:

“Elderly: In a single-dose study (150 mg of Lamictal), the pharmacokinetics of lamotrigine in 12 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.”

Because there was a suggestion from one previous study that there were changes in clearance in the elderly, our Not Approvable letter asked the sponsor to investigate the issue further. Instead, the sponsor has chosen to alter current labeling to de-emphasize the direct comparison of PK and to encourage conservative dosing in the elderly.

Conclusions

The proposed labeling changes more accurately reflect our understanding of the use of Lamictal in the elderly and should be approved.

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

/s/

John Feeney
5/25/01 09:37:42 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

**Review of Response to Not Approvable Letter concerning
Geriatric Use**

NDA (Serial Number)	20-241/S-011 20-764/S-005
Sponsor:	Glaxo Smith Kline
Drug:	Lamictal (lamotrigine) Dispersible Tablets Lamictal (lamotrigine) Chewable Dispersible Tablets
Proposed Indication:	Geriatric Use Labeling Language
Material Submitted:	Response to Not Approvable Letter and Proposed Labeling Changes concerning Geriatric Use
Correspondence Date:	November 27, 2000
Date Received Agency:	November 28, 2000
Date Review Completed	May 21, 2001
Reviewer:	Philip H. Sheridan, M.D.

1. Background

This "Response to Not Approvable Letter and Proposed Labeling Changes" concerning Geriatric Use is the Sponsor's response to the Agency's letter of August 24, 2000.

The above referenced supplemental drug applications were dated August 20, 1999 and were received by the Agency on November 4, 1999. They provided clinical data in support of a labeling revision to update the Geriatric Use subsection of the Lamictal package insert. They proposed to include standard language contained in paragraph (B) under the 21 CFR 201.57 (f) (10) (ii) which states basically that no differences in safety or effectiveness have been observed between elderly and younger subjects. The Agency reviews by Dr. Hershkowitz (August 23, 2000), Dr. Feeney (August 24, 2000), and Dr. Katz (August 24, 2000) concluded that the information provided by the Sponsor in the above referenced supplemental drug applications was inadequate to support the proposed revision; the Agency issued a Not Approvable letter on August 24, 2000.

APPEARS THIS WAY
ON ORIGINAL

The Agency's Not Approvable letter of August 24, 2000 recommended that the Geriatric Use subsection language be amended to read:

“Geriatric Use: Clinical studies of Lamictal 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.”

The Agency's letter also recommended that the Sponsor further evaluate any potential differences between the pharmacokinetics of Lamictal in elderly and younger adults.

This November 27, 2000 Response from the Sponsor agrees to use the Agency's exact, suggested language for the Geriatric Use subsection of PRECAUTIONS.

The Sponsor states its contention that Study UK 72 (12 elderly volunteers in a single dose study of 150 mg of Lamotrigine) in comparison with the aggregate of single dose studies in younger adults (presented in the original application for LANICTAL Tablets) adequately compares the pharmacokinetics of lamotrigine in these two age groups. As a compromise, the Sponsor suggests that the language of the reference to Study UK 72 in the CLINICAL PHARMACOLOGY section be revised to simply present the results of the study without retaining the current labeling's reference to the similarity to single dose studies in younger adults. Specifically, the Sponsor proposes to revise this language as follows:

“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 43.3 hours and the mean clearance was 0.40 mL/min/kg (range 0.26 to 0.48 mL/min/kg).”

Financial Disclosure Information:

The Sponsor's current Response does not present any new study data. Financial Disclosure Information relevant to the studies cited in the Response was provided by the Sponsor in their August 20, 1999 submission (Special Supplement to NDA 20-241 and NDA20-764, Volume 1, Section 1, Pages 5-6). The Sponsor indicates that the study investigators' compensation was not based on the outcome of the studies and that the study investigators had no proprietary interest in Lamictal. Based on this information, it appears unlikely that the study results were biased by financial considerations.

2. Reviewer's Comments:

PRECAUTIONS, Geriatric Use subsection:

The Sponsor has accepted the word-for-word language proposed by the Agency for the Geriatric Use subsection of PRECAUTIONS which now advocates caution in dosing elderly individuals.

CLINICAL PHARMACOLOGY, Elderly:

The Sponsor is proposing to revise the currently existing labeling in the CLINICAL PHARMACOLOGY section to simply indicate that the small elderly volunteer study gives a clearance of 0.40 mL/min/kg. The language no longer states that the clearance for elderly adults is similar to that of younger adults. Of course, anyone reading the entire label to determine how this clearance for elderly adults compares to that of younger adults would find that the aggregate of younger adult studies yields essentially the same clearance. And, in my opinion, such a comparison probably reflects reality for most, but not all, elderly patients.

Therefore the Sponsor's revised language is true as far as it goes, but it stops short of fully elucidating the situation. The proposed revised language does not indicate that two parallel UK studies of single dose kinetics in 12 elderly and 12 younger adults suggested that the clearance in the elderly might be 33% less than in the younger adults. This finding is explicitly discussed in the Agency's Not Approvable letter of August 24, 2000 as the basis for requesting further evaluation of the potential differences between pharmacokinetics in elderly and younger adults.

The Sponsor is understandably reluctant to conduct further studies of lamotrigine pharmacokinetics in the elderly population. Thus the Sponsor has chosen to present the data in labeling in a manner that does not seem to demand further studies but, at the same time, does warn explicitly or implicitly that caution in the face of insufficient data is needed for dosing in elderly patients.

In my opinion, this is a reasonable labeling approach. Even if a larger, single study including younger adults and elderly adults showed the same mean clearance for both groups, more caution should be used in treating any individual elderly patient precisely because of "the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy" encountered in the elderly population. In my opinion, such a larger study might allow more scientifically rigorous labeling language but would not significantly change the safety of clinical dosing of individual elderly patients.

Philip H. Sheridan, MD, HFD-120 Medical Reviewer
20-241/S-011 and 20-764/S-005
Lamictal (lamotrigine) Dispersible and Dispersible Chewable Tablets, Glaxo Smith Kline

3. Conclusion

The currently proposed labeling language for the Geriatric Use subsection of PRECAUTIONS and for the current labeling language for the elderly paragraph of the CLINICAL PHARMACOLOGY section is an acceptable response to the Not Approvable letter.

Philip Sheridan, M. D.
Medical Reviewer

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Philip Sheridan
5/25/01 09:45:49 AM
MEDICAL OFFICER

John Feeney
5/25/01 09:51:59 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-241/S-011

20-764/S-005

CHEMISTRY REVIEW(S)

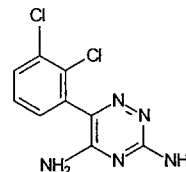
**CHEMIST'S REVIEW
OF SUPPLEMENT**

ORGANIZATION: HFD-120
NDA NUMBER: 20-764
SUPPLEMENT NUMBER: SE8-005
RESPONSE TO NA LETTER 24-AUG-00
AMENDMENT (AL):
LETTER DATE 27-NOV-00
STAMP DATE 28-NOV-00
RECEIVED BY CHEMIST: 02-APR-01

APPLICANT NAME AND ADDRESS: Glaxo Wellcome Inc.
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

NAME OF DRUG: **LAMICTAL®**
NONPROPRIETARY NAME: lamotrigine
CHEMICAL NAME / STRUCTURE: 3,5 diamino-6-(2,3-dichlorophenyl)-as-triazine
DOSAGE FORM(S): CD Tablets
POTENCY(IES): 2, 5, 25 mg
PHARMACOLOGICAL CATEGORY: Anticonvulsant.
Adjunctive treatment of partial seizures in adults and
pediatrics; adjunctive treatment of Lennox Gastaut Syndrome

SPECIAL PRODUCTS: (YES) XX (NO)
HOW DISPENSED: XX (Rx) (OTC)
RECORDS / REPORTS CURRENT: XX (YES) (NO)
RELATED IND / NDA / DMF(s): NDA 20-241 [Tablets]



SUPPLEMENT PROVIDES FOR: Update of the Geriatric Use subsection of the LAMICTAL® Tablets Package Insert as provided for in 21 CFR 201.57(10).

COMMENTS: Response to the FDA Not Approvable Letter of 24-AUG-00 addresses clinical and pharmacokinetic labeling issues for geriatric use. There are no CMC issues in the submission. The PI is the approved on 8-SEP-00. The marketed strengths of Lamictal CD Tablets are 2, 5, 25, mg. One label remains in use for both products Lamictal CD Tablets and Lamictal Tablets. See also N20-241/SE8-011.

Package Insert (PI):

"Description" Section: NO CHANGES since the approved labeling on 8-SEP-00.

"How Supplied" Section: NO CHANGES since the approved labeling on 8-SEP-00.

CONCLUSIONS AND RECOMMENDATIONS: CMC remains as approved.

REVIEWER NAME	SIGNATURE	DATE COMPLETED
Danae Christodoulou, Ph.D.		April 3, 2001

cc: Orig.; NDA 20-764
HFD-120/Div. File
HFD-120/JWare
HFD-120/MMille
HFD-120/DChristodoulou
INIT: MGuzewska/

Filename: N20764SE8.005.doc

/s/

Danae Christodoulou
4/4/01 10:13:52 AM
CHEMIST

Maryla Guzewska
4/5/01 03:49:30 PM
CHEMIST

**APPEARS THIS WAY
ON ORIGINAL**

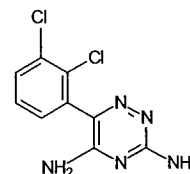
**CHEMIST'S REVIEW
OF SUPPLEMENT**

ORGANIZATION: HFD-120
 NDA NUMBER: 20-241
 SUPPLEMENT NUMBER: SE8-011
 RESPONSE TO NA LETTER 24-AUG-00
 AMENDMENT (AL):
 LETTER DATE 27-NOV-00
 STAMP DATE 28-NOV-00
 RECEIVED BY CHEMIST: 02-APR-01

APPLICANT NAME AND ADDRESS: Glaxo Wellcome Inc.
 Five Moore Drive, P.O. Box 13398
 Research Triangle Park, NC 27709

NAME OF DRUG: **LAMICTAL®**
 NONPROPRIETARY NAME: lamotrigine
 CHEMICAL NAME / STRUCTURE: 3,5 diamino-6-(2,3-dichlorophenyl)-as-triazine
 DOSAGE FORM(S): Tablets
 POTENCY(IES): 25, 100, 150, 200 mg
 PHARMACOLOGICAL CATEGORY: Anticonvulsant.
 Adjunctive treatment of partial seizures in adults and
 pediatrics; adjunctive treatment of Lennox Gastaut Syndrome

SPECIAL PRODUCTS: (YES) XX (NO)
 HOW DISPENSED: XX (Rx) (OTC)
 RECORDS / REPORTS CURRENT: XX (YES) (NO)
 RELATED IND / NDA / DMF(s): NDA 20-764 [CD Tablets]



SUPPLEMENT PROVIDES FOR: Update of the Geriatric Use subsection of the LAMICTAL® Tablets Package Insert as provided for in 21 CFR 201.57(10).

COMMENTS: Response to the Not Approvable Letter of 24-AUG-00 addresses clinical and pharmacokinetic labeling issues for geriatric use. There are no CMC issues in the submission. The PI is the approved on 8-SEP-00. The marketed strengths of Lamictal Tablets are 25, 100, 150, 200 mg. The 50 and 250 mg strengths have been approved but not marketed. One label remains in use for both products Lamictal CD Tablets and Lamictal Tablets. See also N20-764/SE8-005.

Package Insert (PI):
 "Description" Section: NO CHANGES since the approved labeling on 8-SEP-00.
 "How Supplied" Section: NO CHANGES since the approved labeling on 8-SEP-00.

CONCLUSIONS AND RECOMMENDATIONS: CMC remains as approved.

REVIEWER NAME	SIGNATURE	DATE COMPLETED
---------------	-----------	----------------

Danae Christodoulou, Ph.D.		April 3, 2001
----------------------------	--	---------------

cc: Orig.; NDA 20-241
 HFD-120/Div. File
 HFD-120/JWare
 HFD-120/MMille
 HFD-120/DChristodoulou
 INIT: MGuzewska/

Filename: N20241SE8.011.doc

/s/

Danae Christodoulou
4/4/01 10:06:36 AM
CHEMIST

Maryla Guzewska
4/5/01 03:31:35 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-241/S-011

20-764/S-005

**ADMINISTRATIVE
DOCUMENTS**

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form.

<p>1. APPLICANT'S NAME AND ADDRESS</p> <p>Glaxo Wellcome Inc. Five Moore Drive Research Triangle Park, NC 27709</p>	<p>3. PRODUCT NAME</p> <p>Lamictal (lamotrigine) Tablets</p>
<p>2. TELEPHONE NUMBER (Include Area Code)</p> <p>(919) 483-2100</p>	<p>4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? Yes IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.</p> <p>IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:</p> <p><input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.</p> <p><input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).</p>
<p>5. USER FEE I.D. NUMBER</p> <p>N/A</p>	<p>6. LICENSE NUMBER / NDA NUMBER</p> <p>NDA 20-241</p>

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input checked="" type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE. (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

FOR BIOLOGICAL PRODUCTS ONLY

<input type="checkbox"/> WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION	<input type="checkbox"/> A CRUDE ALLERGENIC EXTRACT PRODUCT
<input type="checkbox"/> AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY	<input type="checkbox"/> AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT
<input type="checkbox"/> BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

<p>SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE</p> <p><i>Elizabeth McConnell</i> Elizabeth McConnell, Pharm, D.</p>	<p>TITLE</p> <p>Project Director, Regulatory Affairs</p>	<p>DATE</p> <p>August 20, 1999</p>
---	---	---

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CDER GERIATRIC USE SUPPLEMENT

NDA/NUMBER:

20-241

SUPPLEMENT/NUMBER:

SLR-011

LETTER DATE:

8-20-99

SUPPLEMENT SUBMITTED UNDER 21 CFR 201.57(f)(10)

(See back of form for complete definitions.)

PLEASE CHECK ALL THAT APPLY

- (i)
- (ii)
- (iii)
- (iv)
- (v)
- (vi)
- (vii)

CLINICAL EFFICACY TRIALS:

- Raw data/Study Analyses
- Not Applicable
- Literature

PHARMACOKINETICS AND/OR PHARMACODYNAMICS:

- Raw data/Study Analyses
- Not Applicable
- Literature

SAFETY/ADVERSE REACTIONS: Not Applicable

Clinical Trials:

Anecdotal Report:

- Raw data/Study Analyses
- Literature
- MedWatch/Form 3500
- Literature

OTHER:

PK data to support language in this supplement was submitted as part of the original pharmacokinetic studies in the original NDA.

PROJECT MANAGER:

Jackie Ware

DATE:

9/10/99

PLEASE COMPLETE THIS FORM AND RETURN TO THE DOCUMENT ROOM FOR DATA ENTRY.

*SL
9-13-99*

NDA # 20-241 DOCUMENT ID/LETTER DATE SLR-011 8-20-99

APPLICANT NAME Glaxo Wellcome

PRODUCT NAME Lamictal (Lamotrigine) Tablets

FORM MUST BE COMPLETED ASAP

1. YES User Fee Cover Sheet Validated?

NOTE TO DOCUMENT ROOM:
PLEASE MAKE THE FOLLOWING CHANGES TO THE COMIS DATA ELEMENTS

APPEARS THIS WAY
ON ORIGINAL

2. YES NO CLINICAL DATA?
[Check YES if contains study reports or literature reports of what are explicitly or implicitly represented by the applicant to be adequate and well-controlled trials. Clinical data do not include data used to modify the labelling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).]

REF IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION?

3. YES NO NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (OTHER THAN BUNDLING)? IF YES, list ALL NDA numbers, review divisions & indicate those for which application fees apply.
NDA # DIVISION FEE NO FEE
N _____ FEE NO FEE
N _____ FEE NO FEE

4. YES NO BUNDLING POLICY APPLIED CORRECTLY? NO DATA ENTRY REQUIRED FOR ELEMENT
[Check YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Check NO if application should be split into more than one application or submitted as an original instead of a supplement. IF NO, list resulting NDA numbers, and review divisions.]
NDA # DIVISION NDA # DIVISION
N _____ N _____

5. P S PRIORITY OR STANDARD?

Jacqui Warr 9/10/99
CSO SIGNATURE/DATE

R. J. ... 9/10/99
SCSO CONCURRENCE SIGNATURE/DATE

COPY DISTRIBUTION: ORIGINAL TO ARCHIVAL AFTER DATA ENTRY, ONE COPY EACH TO DIVISION FILE AND CDER, ASSOCIATE DIRECTOR FOR POLICY HFD-5

NDA # 20241 DOCUMENT ID/LETTER DATE SE8011 - 8/20/99
APPLICANT NAME GLAXO Wellcome, INC.
PRODUCT NAME Lamictal Tablets WF# 3835

FORM MUST BE COMPLETED ASAP

120

1. YES User Fee Cover Sheet Validated?

FDS
11/17

NOTE TO DOCUMENT ROOM:
PLEASE MAKE THE FOLLOWING CHANGES TO THE COMES DATA ELEMENTS

APPEARS THIS WAY
ON ORIGINAL

2. YES NO CLINICAL DATA?
[Check YES if contains study reports or literature reports of what are explicitly or implicitly represented by the applicant to be adequate and well-controlled trials. Clinical data do not include data used to modify the labelling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).]

REF. IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION?

3. YES NO NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (OTHER THAN BUNDLING)? IF YES, list ALL NDA numbers, review divisions & indicate those for which application fees apply.

NDA #	DIVISION	FEE	NO FEE
N _____	_____	_____	_____
N _____	_____	_____	_____

4. YES NO BUNDLING POLICY APPLIED CORRECTLY? NO DATA ENTRY REQUIRED FOR KLEMMENT
[Check YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Check NO if application should be split into more than one application or submitted as an original instead of a supplement. IF NO, list resulting NDA numbers, and review divisions.]

NDA #	DIVISION	NDA #	DIVISION
N _____	_____	N _____	_____

5. P S PRIORITY OR STANDARD?

J. Wade 11/16/99

R. [Signature] 11/16/99

6. CSO SIGNATURE/DATE CSO CONCURRENCE SIGNATURE/DATE

COPY DISTRIBUTION: ORIGINAL TO ARCHIVAL AFTER DATA ENTRY, ONE COPY EACH TO DIVISION FILE AND CDER, ASSOCIATE DIRECTOR FOR POLICY HFD-5

Redacted

5

emails

Page(s) of trade

secret and /or

confidential

commercial

information

MEMORANDUM

DATE: May 24, 2001

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-241/S-011 & NDA 20-764/S-005

SUBJECT: Proposed Language for Geriatric Use sub-section of labeling for Lamictal tablets and chewable dispersible tablets

On 8/20/99, Glaxo Wellcome Inc. submitted supplements to the NDAs for Lamictal tablets and chewable dispersible tablets for revised language in the Geriatric sub-sections of labeling. We issued a Not Approvable (NA) letter on 8/24/00, rejecting their proposed labeling, and instead recommended language that stated that the experience in the elderly is insufficient to determine if they respond differently than younger adults (their proposal stated that there were no differences in response between the elderly and younger adults).

In addition, we asked, in the NA letter, for a further exploration of the kinetics in the elderly, because data from a "single" study suggested that the clearance in the elderly was about 33% less than in younger adults (0.4 ml/min/kg vs 0.6 ml/min/kg, respectively). While some estimates, based on other studies, of the clearance in younger adults were considerably closer to the estimate in the elderly (current labeling describes the single dose clearance of Lamictal in the normal younger adult as 0.44 ml/min/kg), the estimates of 0.4 and 0.6 in the elderly and younger adults, respectively, were derived from what was essentially a single study, and represented, to us, the best comparative data.

The sponsor responded to the NA letter in a submission dated 11/27/00. They have agreed to adopt our proposed language for the Geriatric Use sub-section of labeling, but have not undertaken additional evaluation of the kinetics in these 2 age groups. Rather, they have proposed to alter the language in the Elderly sub-section of the Clinical Pharmacology section of labeling to, primarily, remove the statement that the clearances in the 2 age groups are similar. Instead, they slightly alter the description of the study from which the clearance data in the elderly were derived, and describe the mean clearance in the elderly as 0.4 ml/min/kg.

This submission has been reviewed by Dr. Philip Sheridan, medical officer (review dated 5/21/01) and Dr. John Feeney, Neurology Team Leader (memo dated 5/21/01). The review team recommends that the application be approved.

Clearly, the sponsor's agreement to adopt the language that we had proposed for the Geriatric Use sub-section of the Precautions section of labeling is acceptable.

Their response to our request to further explore the relative kinetics in the elderly and younger adults is more problematic.

They have not conducted any additional analyses (or studies), nor have they really addressed the question at all. The following constitutes the sponsor's entire response to this portion of the NA letter (except for their amendment of the language in the Elderly sub-section of the Clinical Pharmacology section of labeling):

"We believe that the comparison of the results of Study UK 72 with other single-dose studies in younger adults (as was presented in the original application for LAMICTAL Tablets) was appropriate in evaluating the comparability of the pharmacokinetics of lamotrigine in these age groups."

I have discussed this at length with Drs. Feeney and Sheridan. While we do not believe that the sponsor has fully addressed our concerns, we agree that the sponsor's proposed language on this point is acceptable at this time. The estimate of the clearance in younger adults presented in current labeling (0.44 ml/min/kg) is the result of analyses of data from numerous studies, and it is not inappropriate to include it in labeling. The estimate of the clearance in the younger adults (0.6 ml/min/kg) derived from the "same" study as the elderly clearance is one realization of the clearance, and it could be argued that the estimate derived from the multiple studies is the more appropriate clearance to be described in labeling. The estimate of the clearance in the elderly derived from that single study represents the only estimate available in this group at this time; it too should be described in labeling.

Further, as Dr. Sheridan notes, labeling will now (in the Geriatric Use sub-section of Precautions) inform prescribers that the elderly should be treated with caution in any event (independent of clearance). For these reasons, then, I find the proposed language acceptable.

However, we still believe that we cannot ignore the fact that the "same" study of elderly and younger adults provides the most direct comparison of the estimate of the clearances, and in this study they differ significantly. Further, the sponsor did not adequately address our concerns on this point expressed in the NA letter. For this reason, we will again ask the sponsor to address this issue.

APPEARS THIS WAY
ON ORIGINAL

ACTION

I will issue the attached Approval letter. In this letter, we will ask the sponsor again to address the question of the relative clearances in elderly and younger adult patients.

Russell Katz, M.D.

APPEARS THIS WAY
ON ORIGINAL

**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
5/25/01 08:16:47 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 20-764 SUPPL # 005
Trade Name Lamictal Chewable Dispersible Tablet
Generic Name lamotrigine
Applicant Name Glaxo Wellcome HFD- 120
Approval Date May 25, 2001

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA? YES/___/ NO /_X_/

b) Is it an effectiveness supplement? YES /___/ NO /_X_/

If yes, what type(SE1, SE2, etc.)? _____

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 /_X_/

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:

A change in the Geriatrics section of labeling was provided for in this supplement; data did not support labeling changes as proposed by the applicant.

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /__X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /___/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

**APPEARS THIS WAY
ON ORIGINAL**

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 # _____

**APPEARS THIS WAY
ON ORIGINAL**

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 # _____

APPEARS THIS WAY
ON ORIGINAL

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S 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 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (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 9:**

- (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:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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 /___/

Investigation #3 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:

NDA # _____ Study # _____
 NDA # _____ Study # _____
 NDA # _____ Study # _____

(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 /___/
 Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
 NDA # _____ Study # _____
 NDA # _____ Study # _____

(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"):

Investigation #__, Study # _____
 Investigation #__, Study # _____
 Investigation #__, Study # _____

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 # _____	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 /___/ Explain _____		!	NO /___/ Explain _____
_____		!	_____
_____		!	_____
		!	_____
Investigation #2	!		
	!		
YES /___/ Explain _____		!	NO /___/ Explain _____
_____		!	_____
_____		!	_____
		!	_____

(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: _____

Signature of Preparer
Title: _____

Date

Signature of Office or Division Director

Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

**APPEARS THIS WAY
ON ORIGINAL**

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Jackie Ware
6/28/01 05:49:32 PM

Russell Katz
6/29/01 07:45:55 AM

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 20-241 SUPPL # 011
Trade Name Lamictal Tablet Generic Name lamotrigine
Applicant Name Glaxo Wellcome HFD- 120
Approval Date May 25, 2001

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA? YES/___/ NO /_X_/

b) Is it an effectiveness supplement? YES /___/ NO /_X_/

If yes, what type(SE1, SE2, etc.)? _____

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 /_X_/

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:

A change in the Geriatrics section of labeling was provided for in this supplement; data did not support labeling changes as proposed by the applicant.

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /__X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /___/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S 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 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (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 9:**

- (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:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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 /___/

Investigation #3 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:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

- (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 /___/
Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

**APPEARS THIS WAY
ON ORIGINAL**

- (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"):

Investigation #__, Study # _____
Investigation #__, Study # _____
Investigation #__, Study # _____

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 # _____ YES /___/ ! NO /___/ Explain: _____
!
!
!
!
!

Investigation #2 !
!
IND # _____ YES /___/ ! NO /___/ Explain: _____
!
!
! APPEARS THIS WAY
! ON ORIGINAL
!
!

(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 /___/ Explain _____ ! NO /___/ Explain _____
!
!
!
!
!

Investigation #2 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____
!
!
!
!
!

(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: _____

Signature of Preparer
Title: _____

Date

Signature of Office or Division Director

Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

**APPEARS THIS WAY
ON ORIGINAL**

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Jackie Ware
6/28/01 05:43:22 PM

Russell Katz
6/29/01 07:43:28 AM

APPEARS THIS WAY
ON ORIGINAL

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-241/S-011

20-764/S-005

CORRESPONDENCE

REVIEW COPY



GlaxoSmithKline

June 18, 2001

Russell G. Katz, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
HFD-120, WOC2, Room 4049
1451 Rockville Pike
Rockville, MD 20852

GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709
Tel. 919 483 2100
www.gsk.com

CENTER FOR DRUG EVALUATION
AND RESEARCH

JUN 19 2001

RECEIVED HFD-120

DUPLICATE

NDA SUPP AMEND
SE8-011-FA

Re: NDA 20-241/S-011; LAMICTAL® (lamotrigine) Tablets
NDA 20-764/S-005; LAMICTAL® (lamotrigine) Chewable Dispersible Tablets
General Correspondence: Labeling-FPL for approved supplements

SE8-005F

Dear Dr. Katz:

Reference is made to the aforementioned supplemental new drug applications submitted on August 20, 1999, to update the Geriatric Use subsection of the LAMICTAL Tablets and LAMICTAL Chewable Dispersible Tablets labeling. Reference is also made to the Agency's approval letter of May 25, 2001.

As requested in the approval letter, we are providing 20 paper copies of final printed labeling. The package insert copy is identical to the copy included with the approval letter except that it includes revisions to the CLINICAL PHARMACOLOGY, PRECAUTIONS, and DOSAGE AND ADMINISTRATION sections as outlined in the "Special Supplement: Changes Being Effected" submitted February 8, 1999 (NDA 20-241/S-010 and NDA 20-764/S-003).

If you have any questions regarding this submission, please do not hesitate to contact me at (919) 483-6466.

Sincerely,

Elizabeth A. McConnell, Pharm.D.
Project Director
Regulatory Affairs

CSO Note: NAT
FA Succeeded.
June 6/10/03

June 18, 2001



GlaxoSmithKline

Russell G. Katz, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
HFD-120, WOC2, Room 4049
1451 Rockville Pike
Rockville, MD 20852

CENTER FOR DRUG EVALUATION
AND RESEARCH

JUN 19 2001

RECEIVED HFD-120

GlaxoSmithKline

PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709

Tel. 919 483 2100
www.gsk.com

ORIGINAL

NDA SUPP AMEND

Re: NDA 20-241/S-011; LAMICTAL® (lamotrigine) Tablets
NDA 20-764/S-005; LAMICTAL® (lamotrigine) Chewable Dispersible Tablets
General Correspondence: Labeling-FPL for approved supplements

SK8-011 (FA)

Dear Dr. Katz:

Reference is made to the aforementioned supplemental new drug applications submitted on August 20, 1999, to update the Geriatric Use subsection of the LAMICTAL Tablets and LAMICTAL Chewable Dispersible Tablets labeling. Reference is also made to the Agency's approval letter of May 25, 2001.

As requested in the approval letter, we are providing 20 paper copies of final printed labeling. The package insert copy is identical to the copy included with the approval letter except that it includes revisions to the CLINICAL PHARMACOLOGY, PRECAUTIONS, and DOSAGE AND ADMINISTRATION sections as outlined in the "Special Supplement: Changes Being Effected" submitted February 8, 1999 (NDA 20-241/S-010 and NDA 20-764/S-003).

If you have any questions regarding this submission, please do not hesitate to contact me at (919) 483-6466.

Sincerely,

Elizabeth A. McConnell, Pharm.D.
Project Director
Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338.
Expiration Date: April 30, 2000.
See OMB Statement on last page.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN
ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT

Glaxo Wellcome Inc.

DATE OF SUBMISSION

June 18, 2001

TELEPHONE NO. (Include Area Code)

(919) 483-2100

FACSIMILE (FAX) Number (Include Area Code)

(919) 483-5063

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code and U.S. License number if previously issued):

**Five Moore Drive
Research Triangle Park, NC 27709**

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)

20-241/S-011

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)

Lamotrigine

PROPRIETARY NAME (trade name) IF ANY

Lamictal® Tablets

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)

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

CODE NAME (If any)

BW430C

DOSAGE FORM:

Tablets

STRENGTHS:

25mg, 100mg, 150mg, 200mg

ROUTE OF ADMINISTRATION:

Oral

(PROPOSED) INDICATION(S) FOR USE

**Adjunctive treatment of partial seizures in adults and pediatrics
Adjunctive treatment of Lennox Gastaut Syndrome**

APPLICATION INFORMATION

APPLICATION TYPE

(check one)

NEW DRUG APPLICATION (21 CFR 314.50)

ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)

BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

505 (b) (1)

505 (b) (2)

507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug

Holder of Approved Application

TYPE OF SUBMISSION

(check one)

ORIGINAL APPLICATION

AMENDMENT TO A PENDING APPLICATION

RESUBMISSION

PRESUBMISSION

ANNUAL REPORT

ESTABLISHMENT DESCRIPTION SUPPLEMENT

SUPAC SUPPLEMENT

EFFICACY SUPPLEMENT

LABELING SUPPLEMENT

CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

OTHER

REASON FOR SUBMISSION

General Correspondence: Labeling-FPL for approved supplements

PROPOSED MARKETING STATUS (check one)

PRESCRIPTION PRODUCT (Rx)

OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED

1

THIS APPLICATION IS

PAPER

PAPER AND ELECTRONIC

ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (Check all that apply)		
	1. Index	
X	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input checked="" type="checkbox"/> Final Printed Labeling	
	3. Summary (21 CFR 314.50 (c))	
	4. Chemistry section	
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)	
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
	C. Methods Validation Package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)	
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2), 21 CFR 601.2)	
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3), 21 CFR 601.2)	
	7. Clinical Microbiology (21 CFR 314.50 (d) (4))	
	8. Clinical data section (21 CFR 314.50 (d) (5))	
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)	
	10. Statistical section (21 CFR 314.50 (d) (6), 21 CFR 601.2)	
	11. Case report tabulations (21 CFR 314.50 (f) (1), 21 CFR 601.2)	
	12. Case reports forms (21 CFR 314.50 (f) (2), 21 CFR 601.2)	
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))	
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))	
	15. Establishment description (21 CFR Part 600, if applicable)	
	16. Debarment certification (FD&C Act 306 (k)(1))	
	17. Field copy certification (21 CFR 314.5 (K) (3))	
	18. User Fee Cover Sheet (Form FDA 3397)	
	19. OTHER (Specify)	
CERTIFICATION I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following: <ol style="list-style-type: none"> 1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820. 2. Biological establishment standards in 21 CFR Part 600. 3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809. 4. In the case of a prescription drug or biologic product, prescription drug advertising regulations in 21 CFR 202. 5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99 and 601.12. 6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81. 7. Local, state and Federal environmental impact laws. If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision. The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate. Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.		
SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Elizabeth A. McConnell, Pharm.D. Project Director, Regulatory Affairs	June 18, 2001
ADDRESS (Street, City, State, and ZIP Code)		Telephone Number
Five Moore Drive Research Triangle Park, NC 27709		(919) 483-6466
Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:		
DHHS, Reports Clearance Officer Paperwork Reduction Project (0910-0338) Hubert H. Humphrey Building, Room 531-H 200 Independence Avenue, S.W. Washington, DC 20201		An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
Please DO NOT RETURN this form to this address.		

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS Glaxo Wellcome Inc. Five Moore Drive Research Triangle Park, NC 27709	3. PRODUCT NAME LAMICTAL (lamotrigine) Tablets
2. TELEPHONE NUMBER (Include Area Code) (919) 483-2100	4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? No IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).
5. USER FEE I.D. NUMBER	6. LICENSE NUMBER / NDA NUMBER NDA 20-241/S-011

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input checked="" type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE. (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

FOR BIOLOGICAL PRODUCTS ONLY

<input type="checkbox"/> WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION	<input type="checkbox"/> A CRUDE ALLERGENIC EXTRACT PRODUCT
<input type="checkbox"/> AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY	<input type="checkbox"/> AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT
<input type="checkbox"/> BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See reverse side if answered YES)


A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE  Elizabeth A. McConnell, Pharm. D.	TITLE Project Director, Regulatory Affairs	DATE June 18, 2001
---	--	------------------------------

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

In 169 patients with Lennox-Gastaut syndrome (26 patients were between the ages of 16 and 25), 3.8% of patients on LAMICTAL and 7.8% 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 10% of the 1136 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 (3.9%), reaction aggravated (1.7%), and ataxia (0.9%).

Incidence in Controlled Clinical Studies: 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: 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 patients' current AED therapy. Adverse events were usually mild to moderate in intensity.

Table 4: Treatment-Emergent Adverse Event Incidence in Placebo-Controlled Adjunctive Trials*
 (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 one to three concomitant EIAEDs 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

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

*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.

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

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 2% 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 in a Controlled Monotherapy Trial* (Events in at least 2% of patients treated with LAMICTAL and numerically more frequent than in the valproate [VPA] group.)

Body System/ Adverse Experience†	Percent of Patients Receiving LAMICTAL Monotherapy‡ (n = 43)	Percent of Patients Receiving Low-Dose VPA§ Monotherapy (n = 44)
Body as a whole		
Pain	5	0
Infection	5	2
Chest pain	5	2
Asthenia	2	0
Fever	2	0
Digestive		
Vomiting	9	0
Dyspepsia	7	2
Nausea	7	2
Anorexia	2	0
Dry mouth	2	0
Rectal hemorrhage	2	0
Peptic ulcer	2	0
Metabolic and nutritional		
Weight decrease	5	2
Peripheral edema	2	0
Nervous		
Coordination abnormality	7	0
Dizziness	7	0
Anxiety	5	0
Insomnia	5	2
Amnesia	2	0
Ataxia	2	0
Depression	2	0
Hypesthesia	2	0
Libido increase	2	0
Decreased reflexes	2	0
Increased reflexes	2	0
Nystagmus	2	0
Irritability	2	0
Suicidal ideation	2	0
Respiratory		
Rhinitis	7	2
Epistaxis	2	0
Bronchitis	2	0
Dyspnea	2	0
Skin and appendages		
Contact dermatitis	2	0
Dry skin	2	0
Sweating	2	0
Special senses		
Vision abnormality	2	0
Urogenital (female patients only)		
Dysmenorrhea	(n = 21) 5	(n = 28) 0

*Patients in these studies were converted to LAMICTAL or VPA 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 2% of patients are included.

‡Up to 500 mg/day.

§1000 mg/day.

Incidence in a Controlled Adjunctive Trial in Adult and Pediatric Patients With Lennox-Gastaut Syndrome: Table 7 lists adverse events that occurred in at least 2% of 79 adult and pediatric patients who received LAMICTAL up to 15 mg/kg per day or a maximum of 400 mg per day. Reported adverse events were classified using COSTART terminology.

Table 7: Treatment-Emergent Adverse Event Incidence in Placebo-Controlled Adjunctive Trial in Adult and Pediatric Patients With Lennox-Gastaut Syndrome (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 = 79)	Percent of Patients Receiving Placebo (n = 90)
Body as a whole		
Infection	13	8
Accidental injury	9	7
Flu syndrome	5	0
Asthenia	3	1
Abdominal pain	3	0
Cardiovascular		
Hemorrhage	3	0
Digestive		
Vomiting	9	7
Constipation	5	2
Diarrhea	4	2
Nausea	4	1
Anorexia	3	1
Nervous system		
Ataxia	4	1
Convulsions	4	1
Tremor	3	0

(continued on next column)

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

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. **Adjunctive Therapy With LAMICTAL:** 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 whether or not the patient is receiving VPA (Tables 8 and 9 for patients 2 to 12 years of age, Tables 10 and 11 for patients greater than 12 years of age). In addition, the section provides a discussion of dosing for those patients receiving concomitant AEDs that have not been systematically evaluated in combination with LAMICTAL.

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

Patients 2 to 12 Years of Age: Recommended dosing guidelines for LAMICTAL added to an antiepileptic drug (AED) regimen containing VPA are summarized in Table 8. Recommended dosing guidelines for LAMICTAL added to EIAEDs are summarized in Table 9.

LAMICTAL Added to AEDs Other Than EIAEDs and VPA: The effect of AEDs other than EIAEDs and VPA on the metabolism of LAMICTAL is not currently known. Therefore, no specific dosing guidelines can be provided in that situation. Conservative starting doses and dose escalations (as with concomitant VPA) would be prudent; maintenance dosing would be expected to fall between the maintenance dose with VPA and the maintenance dose without VPA, but with an EIAED.

Note that the starting doses and dose escalations listed below 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. It is likely that patients aged 2 to 6 years will require a maintenance dose at the higher end of the maintenance dose range.

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 LAMICTAL Chewable Dispersible Tablet available sizes).

Table 8: LAMICTAL Added to an AED Regimen Containing VPA in Patients 2 to 12 Years of Age

Weeks 1 and 2		0.15 mg/kg/day in one or two divided doses, rounded down to the nearest whole tablet. Only whole tablets should be used for dosing.	
Weeks 3 and 4		0.3 mg/kg/day in one or two divided doses, rounded down to the nearest whole tablet.	
Weight based dosing can be achieved by using the following guide:			
If the patient's weight is		Give this daily dose, using the most appropriate combination of Lamictal 2 mg and 5 mg tablets	
Greater than	And less than	Weeks 1 and 2	Weeks 3 and 4
6.7 kg	14 kg	2 mg every 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
Usual maintenance dose: 1 to 5 mg/kg/day (maximum 200 mg/day in one or two divided doses). To achieve the usual maintenance dose, subsequent doses should be increased every 1 to 2 weeks as follows: calculate 0.3 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily dose.			

Table 9: LAMICTAL Added to EIAEDs (Without VPA) in Patients 2 to 12 Years of Age

Weeks 1 and 2	0.6 mg/kg/day in two divided doses, rounded down to the nearest whole tablet.
Weeks 3 and 4	1.2 mg/kg/day in two divided doses, rounded down to the nearest whole tablet.
Usual maintenance dose: 5 to 15 mg/kg/day (maximum 400 mg/day in two divided doses). To achieve the usual maintenance dose, subsequent doses should be increased every 1 to 2 weeks as follows: calculate 1.2 mg/kg/day, round this amount down to the nearest whole tablet, and add this amount to the previously administered daily dose.	

Patients Over 12 Years of Age: Recommended dosing guidelines for LAMICTAL added to VPA are summarized in Table 10. Recommended dosing guidelines for LAMICTAL added to EIAEDs are summarized in Table 11.

LAMICTAL Added to AEDs Other Than EIAEDs and VPA: The effect of AEDs other than EIAEDs and VPA on the metabolism of LAMICTAL is not currently known. Therefore, no specific dosing guidelines can be provided in that situation. Conservative starting doses and dose escalations (as with concomitant VPA) would be prudent; maintenance dosing would be expected to fall between the maintenance dose with VPA and the maintenance dose without VPA, but with an EIAED.

Table 10: LAMICTAL Added to an AED Regimen Containing VPA in Patients Over 12 Years of Age

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

Table 11: LAMICTAL Added to EIAEDs (Without VPA) in Patients Over 12 Years of Age

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

Conversion From a Single EIAED to Monotherapy With LAMICTAL in Patients ≥16 Years of Age: 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 conversion regimen involves two steps. In the first, LAMICTAL is titrated to the targeted dose while maintaining the dose of the EIAED at a fixed level; in the second step, the EIAED is gradually withdrawn over a period of 4 weeks.

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

LAMICTAL should be added to an EIAED to achieve a dose of 500 mg/day according to the guidelines in Table 11 above. The regimen for the withdrawal of the concomitant EIAED is based on experience gained in the controlled monotherapy clinical trial. In that trial, the concomitant EIAED was withdrawn by 20% decrements each week over a 4-week period.

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

Usual Maintenance Dose: The usual maintenance doses identified in the tables above 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 EIAEDs without VPA, maintenance doses of adjunctive LAMICTAL as high as 700 mg/day have been used. In patients receiving VPA alone, maintenance doses of adjunctive LAMICTAL as high as 200 mg/day have been used. The advantage of using doses above those recommended in the tables above has not been established in controlled trials.

Patients With Hepatic Impairment: Experience in patients with hepatic impairment is limited. Based on a clinical pharmacology study in 24 patients with moderate to severe liver dysfunction (see CLINICAL PHARMACOLOGY), the following general recommendations can be made. Initial, escalation, and maintenance doses should generally be reduced by approximately 50% in patients with moderate (Child-Pugh Grade B) and 75% in patients with severe (Child-Pugh Grade C) hepatic impairment. Escalation and maintenance doses should 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).

LAMICTAL[®] (lamotrigine) Tablets

LAMICTAL[®] (lamotrigine) Chewable Dispersible Tablets

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.

Discontinuation Strategy: 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 an EAED should prolong the half-life of lamotrigine; discontinuing VPA should shorten the half-life of lamotrigine.
Target Plasma Levels: A therapeutic plasma concentration range has not been established for lamotrigine. Dosing of LAMICTAL should be based on therapeutic response.

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 GLAXO WELLCOME INC. 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.




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

Information for the Patient

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
--	---	--

NOTE: The pictures above 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. Before taking your medicine, it is important to compare the tablets you receive from your doctor or pharmacist with these pictures to make sure you have received the correct medicine.

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.

1. The Purpose of Your Medicine:

Lamotrigine is intended to be used either alone or in combination with other medicines to treat seizures in people age 16 years or older and/or only those patients below the age of 16 years who have seizures associated with the Lennox-Gastaut syndrome. When taking lamotrigine, it is important to follow your doctor's instructions.

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. The most common side effects with LAMICTAL are dizziness, headache, blurred or double vision, lack of coordination, sleepiness, nausea, vomiting, and rash.
- 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 valproic acid (DEPAKENE[®] or DEPAKOTE[®]), 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 Breast-feeding:

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. 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.
- If you miss a dose of LAMICTAL, do not double your next dose.
- Do NOT stop taking LAMICTAL or any of your other seizure 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.
- Tell your doctor if your seizures get worse or if you have any new types of seizures.

APPEARS THIS WAY
ON ORIGINAL

• Always tell your doctor and pharmacist if you are taking or plan to take any other prescription or over-the-counter medicines.

6. 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.

7. 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. 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.

GlaxoWellcome

Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

DEPAKENE and DEPAKOTE are registered trademarks of Abbott Laboratories.

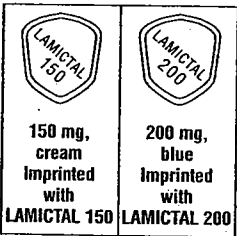
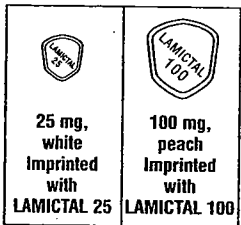
JS Patent No. 4,602,017 and 5,698,226
©Copyright 1998, 1999, 2000, 2001, Glaxo Wellcome Inc. All rights reserved.

May 2001

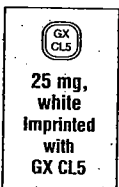
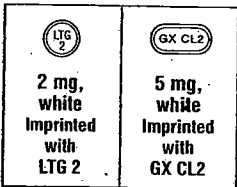
RL-950

Information for the Patient

**LAMICTAL®
(lamotrigine) Tablets**



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



APPEARS THIS WAY
ON ORIGINAL

NOTE: The pictures above 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. Before taking your medicine, it is important to compare the tablets you receive from your doctor or pharmacist with these pictures to make sure you have received the correct medicine.

APPEARS THIS WAY
ON ORIGINAL

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.

1. The Purpose of Your Medicine:

Lamotrigine is intended to be used either alone or in combination with other medicines to treat seizures in people age 16 years or older and/or only those patients below the age of 16 years who have seizures associated with the Lennox-Gastaut syndrome. When taking lamotrigine, it is important to follow your doctor's instructions.

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:

INSTRUCTIONS TO PATIENT

- Most people who take LAMICTAL tolerate it well. The most common side effects with LAMICTAL are dizziness, headache, blurred or double vision, lack of coordination, sleepiness, nausea, vomiting, and rash.
- 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 valproic acid (DEPAKENE® or DEPAKOTE®), 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 Breast-feeding:

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. 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

APPEARS THIS WAY
ON ORIGINAL

**LAMICTAL® (lamotrigine)
Tablets**

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

(cont'd from previous side)

- 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.
- If you miss a dose of lamotrigine, do not double your next dose.
- Do NOT stop taking LAMICTAL or any of your other seizure 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.
- Tell your doctor if your seizures get worse or if you have any new types of seizures.
- Always tell your doctor and pharmacist if you are taking or plan to take any other prescription or over-the-counter medicines.

6. 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.

7. 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. 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.

APPEARS THIS WAY
ON ORIGINAL

GlaxoWellcome

Glaxo Wellcome Inc.
Research Triangle Park,
NC 27709

DEPAKENE and DEPAKOTE
are registered trademarks of
Abbott Laboratories.

US Patent No. 4,602,017 and
5,698,226

©Copyright 1998, 1999, 2000,
2001, Glaxo Wellcome Inc. All
rights reserved.

May 2001
RL-950

APPEARS THIS WAY
ON ORIGINAL

GlaxoWellcome

ORIGINAL

November 27, 2000

CENTER FOR DRUG EVALUATION
AND RESEARCH

NOV 28 2000

RECEIVED HFD-120

Russell G. Katz, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
HFD-120, WOC2, Room 4049
1451 Rockville Pike
Rockville, MD 20852

Re: NDA 20-241/S-011; LAMICTAL® (lamotrigine) Tablets
NDA 20-764/S-005; LAMICTAL® (lamotrigine) Chewable Dispersible Tablets
Response to Not Approvable Letter: Labeling

NDA SUPP AMEND SEC-011-AL

Dear Dr. Katz:

Reference is made to the Agency's August 24, 2000 NOT APPROVABLE letter for the aforementioned supplemental new drug applications. These applications were submitted on August 24, 1999 (and officially filed on November 4, 1999) in order to update the Geriatric Use subsection of the LAMICTAL Tablets package insert as provided for in 21 CFR 201.57(10).

This amendment to these applications is intended to fully respond to the Agency's comments and requests so as to allow for their approval.

First, the Agency recommended that Glaxo Wellcome amend these applications to include the following language in the Geriatric Use subsection of PRECAUTIONS:

Geriatric Use: Clinical studies of LAMICTAL did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection 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.

Glaxo Wellcome agrees to revise the LAMICTAL label as proposed by the Agency.

Second, the Agency requested that Glaxo Wellcome evaluate the comparability of the pharmacokinetics of lamotrigine in elderly and younger adults. We believe that the comparison of the results of Study UK 72 with other single-dose studies in younger

Glaxo Wellcome Inc.

Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709-3398

Telephone
919 483 2100

Russell G. Katz, M.D.

November 27, 2000

Page 2

adults (as was presented in the original application for LAMICTAL Tablets) was appropriate in evaluating the comparability of the pharmacokinetics of lamotrigine in these age groups. However, we propose that current labeling be revised to present the results of Study UK 72 without making reference to any similarity in the pharmacokinetics of lamotrigine between elderly and younger subjects. Specifically, we propose the following revision to the CLINICAL PHARMACOLOGY section:

Age: 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).

This submission contains the following:

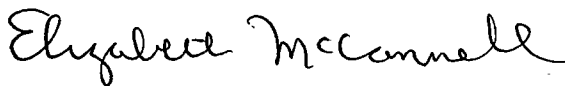
- Proposed labeling with the changes above highlighted in revision marks (**Attachment 1**)
- A clean copy of proposed labeling (**Attachment 2**)
- A diskette containing a WORD 97 version of the unhighlighted labeling (**Attachment 3**)

A desk copy of this submission is being provided to Jacqueline Ware, Pharm.D., under separate cover.

This submission is being filed to NDA 20-241/S-011 and incorporated by reference to NDA 20-764/S-005.

We believe that this response to the Agency's NOT APPROVABLE letter is complete and will allow the Agency to complete the assessment of these applications. If you have any questions regarding this submission, please do not hesitate to contact me at 919-483-6466.

Sincerely,



Elizabeth A. McConnell, Pharm.D.
Project Director
Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN
ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338.
Expiration Date: April 30, 2000.
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT

Glaxo Wellcome Inc.

DATE OF SUBMISSION

November 27, 2000

TELEPHONE NO. (Include Area Code)

(919) 483-2100

FACSIMILE (FAX) Number (Include Area Code)

(919) 483-5063

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code and U.S. License number if previously issued):

**Five Moore Drive
Research Triangle Park, NC 27709**

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)

20-241/S-011

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)

Lamotrigine

PROPRIETARY NAME (trade name) IF ANY

Lamictal® Tablets

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)

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

CODE NAME (If any)

BW430C

DOSAGE FORM:

Tablets

STRENGTHS:

25mg, 100mg, 150mg, 200mg

ROUTE OF ADMINISTRATION:

Oral

(PROPOSED) INDICATION(S) FOR USE

**Adjunctive treatment of partial seizures in adults and pediatrics
Adjunctive treatment of Lennox Gastaut Syndrome**

APPLICATION INFORMATION

APPLICATION TYPE

(check one)

NEW DRUG APPLICATION (21 CFR 314.50)

ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)

BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

505 (b) (1)

505 (b) (2)

507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug

Holder of Approved Application

TYPE OF SUBMISSION

(check one)

ORIGINAL APPLICATION

AMENDMENT TO A PENDING APPLICATION

RESUBMISSION

PRESUBMISSION

ANNUAL REPORT

ESTABLISHMENT DESCRIPTION SUPPLEMENT

SUPAC SUPPLEMENT

EFFICACY SUPPLEMENT

LABELING SUPPLEMENT

CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT

OTHER

REASON FOR SUBMISSION

Response to Not Approvable Letter

PROPOSED MARKETING STATUS (check one)

PRESCRIPTION PRODUCT (Rx)

OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED

1

THIS APPLICATION IS

PAPER

PAPER AND ELECTRONIC

ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (Check all that apply)

	1. Index
X	2. Labeling (check one) <input checked="" type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods Validation Package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (21 CFR 314.50 (d) (4))
	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.5 (K) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) Response to Not Approvable Letter

CERTIFICATION

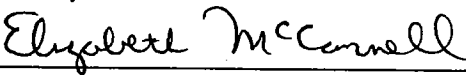
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biologic product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99 and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Elizabeth A. McConnell, Pharm.D. Project Director, Regulatory Affairs	DATE November 27, 2000
ADDRESS (Street, City, State, and ZIP Code) Five Moore Drive Research Triangle Park, NC 27709		Telephone Number (919) 483-6466

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.



61.1

Food and Drug Administration
Rockville MD 20857

~~NDA 20-241/S-01~~
NDA 20-764/S-005

NOV - 8 1999

Glaxo Wellcome Inc.
Attention: Elizabeth A. McConnell, Pharm.D.
Five Moore Drive
Research Triangle Park, NC 27709

Dear Dr. McConnell:

Please refer to your supplemental new drug applications (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Lamictal (lamotrigine) Tablets and Lamictal (lamotrigine) Chewable Dispersible Tablets.

You were notified in our letter dated October 20, 1999, that your applications were not accepted for filing due to non-payment of fees. This is to notify you that the Agency has received all fees owed and your applications have been accepted as of November 4, 1999.

The review priority classification for this application is Standard (S).

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 2, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be September 4, 2000 and the secondary user fee goal date will be November 4, 2000.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug
Products, HFD-120
Attention: Division Document Room 4008
5600 Fishers Lane
Rockville, Maryland 20857

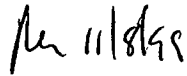
Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug
Products, HFD-120
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, Maryland 20852-1420

NDA 20-241/S-011
NDA 20-764/S-005
Page 2

If you have any questions, contact Jacqueline H. Ware, Pharm.D., Regulatory Management Officer, at (301) 594-5793.

Sincerely,



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

APPEARS THIS WAY
ON ORIGINAL

NDA 20-241/S-011

NDA 20-764/S-005

Page 3

cc:

cc:

Archival NDA 20-241, 20-764

HFD-120 Division file

HFD-120/Ware

HFD-120/Katz/Feeney

HFD-005/Jones/Friedman

DISTRICT OFFICE

Drafted by: jhw/November 4, 1999

Initialed by:

final:

filename: C:\My Documents\WPFILES\jwndas\N20241\S011\ACLTR.DOC

ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY
ON ORIGINAL

GlaxoWellcome

NDA SUPP AMEND *SNC-011*

November 1, 1999

DUPLICATE

NEW CORRESP

Russell G. Katz, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
HFD-120, WOC2, Room 4049
1451 Rockville Pike
Rockville, MD 20852

CENTER FOR DRUG EVALUATION
AND RESEARCH

NOV 02 1999

RECEIVED HFD-120

Re: ~~NDA 20-241/S-011; LAMICTAL® (lamotrigine) Tablets~~
NDA 20-764/S-005; LAMICTAL® (lamotrigine) Chewable Dispersible Tablets
User Fee: With Clinical Data

Dear Dr. Katz:

Reference is made to the aforementioned supplements submitted to the Agency on August 20, 1999. Reference is also made to the Agency's letter of October 20, 1999 stating that these applications were not accepted for filing because it was determined that the applications required a user fee.

Appended are copies of the FDA Form 3397 and the user fee check for these applications. The user fee applies to both supplements as the clinical data supporting the proposed label changes has been filed to NDA 20-241 and incorporated by reference to NDA 20-764. It is our understanding that the applications will be accepted for filing as soon as the Agency is notified of the receipt of the user fee. Per the Agency's letter of October 20, 1999, these supplements will require approval before labeling changes can be implemented.

APPEARS THIS WAY
ON ORIGINAL

Glaxo Wellcome Inc.

Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

Telephone
919 483 2100

*Cso Note: ~~XXXX~~
Fee received & application
accepted 11/4/99. See
Acc letter. Jwore
11/30/99*

GlaxoWellcome

November 1, 1999

Bank Mellon, N/A
Bank @ FDA
Food and Drug Administration
27th Floor (FDA 360909)
Three Mellon Bank Center
Pittsburgh, PA 15259-0001

Re: NDA 20-241/S-011; LAMICTAL® (lamotrigine) Tablets
NDA 20-764/S-005; LAMICTAL® (lamotrigine) Chewable Dispersible Tablets
User Fee No. 3835

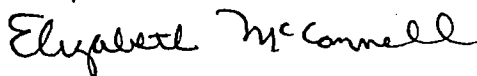
Please find enclosed Glaxo Wellcome check number 0002970 in the amount of \$136,141.00. This is the application fee for the supplemental New Drug Applications listed above that were filed on August 20, 1999 with the Center for Drug Evaluation and Research, FDA. The original supplement was submitted to NDA 20-241, LAMICTAL Tablets and incorporated by reference to NDA 20-764, LAMICTAL Dispersible Tablets; therefore, only one user fee identification number was obtained.

Please find below requested information regarding this application

Type of Application:	New Drug Application with Clinical Data	
	New Drug Application without Clinical Data	
	Supplemental New Drug Application with Clinical Data	X

Should you have any questions, please contact me at (919) 483-6466.

Sincerely,



Elizabeth A. McConnell, Pharm.D.
Project Director
Regulatory Affairs

Glaxo Wellcome Research and Development

Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709-3398

Telephone
919 483 2100

A Division of
Glaxo Wellcome Inc.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS Glaxo Wellcome Inc. Five Moore Drive Research Triangle Park, NC 27709	3. PRODUCT NAME LAMICTAL® (lamotrigine) Tablets
2. TELEPHONE NUMBER (Include Area Code) (919) 483-2100	4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? Yes IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).
5. USER FEE I.D. NUMBER 3835	6. LICENSE NUMBER / NDA NUMBER NO20241

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE. (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	
FOR BIOLOGICAL PRODUCTS ONLY	
<input type="checkbox"/> WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION	<input type="checkbox"/> A CRUDE ALLERGENIC EXTRACT PRODUCT
<input type="checkbox"/> AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY	<input type="checkbox"/> AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT
<input type="checkbox"/> BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE  Elizabeth A. McConnell, Pharm.D..	TITLE Project Director, Regulatory Affairs	DATE November 1, 1999
---	--	---------------------------------

GlaxoWellcome

~~NDA SUPPLEMENT~~

NEW CORRESP

NC (SE8011)

November 1, 1999

ORIGINAL

Russell G. Katz, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
HFD-120, WOC2, Room 4049
1451 Rockville Pike
Rockville, MD 20852

CENTER FOR DRUG EVALUATION
AND RESEARCH

NOV 02 1999

RECEIVED HFD-120

Re: NDA 20-241/S-011; LAMICTAL® (lamotrigine) Tablets
NDA 20-764/S-005; LAMICTAL® (lamotrigine) Chewable Dispersible Tablets
User Fee: With Clinical Data

Dear Dr. Katz:

Reference is made to the aforementioned supplements submitted to the Agency on August 20, 1999. Reference is also made to the Agency's letter of October 20, 1999 stating that these applications were not accepted for filing because it was determined that the applications required a user fee.

Appended are copies of the FDA Form 3397 and the user fee check for these applications. The user fee applies to both supplements as the clinical data supporting the proposed label changes has been filed to NDA 20-241 and incorporated by reference to NDA 20-764. It is our understanding that the applications will be accepted for filing as soon as the Agency is notified of the receipt of the user fee. Per the Agency's letter of October 20, 1999, these supplements will require approval before labeling changes can be implemented.

APPEARS THIS WAY
ON ORIGINAL

Glaxo Wellcome Inc.

Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

Telephone
919 483 2100

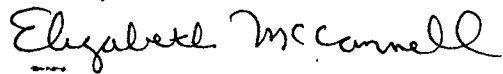
Russell G. Katz, M.D.

November 1, 1999

Page 2

A desk copy of this submission is being provided to Jacqueline Ware, Pharm.D., Regulatory Management Officer, under separate cover. If you have any questions regarding this submission, please contact me at 919-483-6466.

Sincerely,



Elizabeth A. McConnell, Pharm.D.

Project Director

Regulatory Affairs

Cc: Jacqueline Ware, Pharm.D., Regulatory Management Officer, HFD-120

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338.
Expiration Date: April 30, 2000.
See OMB Statement on last page.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN
ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Glaxo Wellcome Inc.		DATE OF SUBMISSION November 1, 1999
TELEPHONE NO. (Include Area Code) (919) 483-2100		FACSIMILE (FAX) Number (Include Area Code) (919) 483-5063
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code and U.S. License number if previously issued): Five Moore Drive Research Triangle Park, NC 27709		AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)		20-241
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Lamotrigine	PROPRIETARY NAME (trade name) IF ANY Lamictal® Tablets	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) 3,5-diamino-6-(2,3-dichlorophenyl)-as-triazine		CODE NAME (If any) BW430C
DOSAGE FORM: Tablets	STRENGTHS: 25mg, 100mg, 150mg, 200mg	ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE

**Adjunctive treatment of partial seizures in pediatrics
Adjunctive treatment of Lennox Gastaut Syndrome**

APPLICATION INFORMATION

APPLICATION TYPE (check one)		
<input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)	<input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)	
<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)		
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b) (1) <input type="checkbox"/> 505 (b) (2) <input type="checkbox"/> 507		
IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug: _____ Holder of Approved Application: _____		
TYPE OF SUBMISSION (check one)		
<input type="checkbox"/> ORIGINAL APPLICATION	<input type="checkbox"/> AMENDMENT TO A PENDING APPLICATION	<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> PRESUBMISSION	<input type="checkbox"/> ANNUAL REPORT	<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT
<input type="checkbox"/> EFFICACY SUPPLEMENT	<input type="checkbox"/> LABELING SUPPLEMENT	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT
		<input checked="" type="checkbox"/> OTHER

REASON FOR SUBMISSION

User Fee

PROPOSED MARKETING STATUS (check one)	<input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx)	<input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED <u>1</u>	THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER	<input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

GlaxoWellcome

October 21, 1999

NEW CORRESP

MC
DUPLICATE

Russell G. Katz, M.D., Acting Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
HFD-120, WOC2, Room 4049
1451 Rockville Pike
Rockville, MD 20852

CENTER FOR DRUG EVALUATION
AND RESEARCH

OCT 22 1999

RECEIVED HFD-120

Re: NDA 20-241/S-011; LAMICTAL® (lamotrigine) Tablets
NDA 20-764/S-005; LAMICTAL® (lamotrigine) Chewable Dispersible Tablets
General Correspondence: Response to Unacceptability for Filing Letter

Dear Dr. Katz:

Reference is made to the aforementioned applications which were submitted on August 20, 1999 as "Special Supplements: Changes Being Effected" in compliance with the requirements for the *Geriatric Use* subsection of prescription drug labeling as described in 21 CFR 201.57 (f)(10).

Reference is also made to a telephone conversation with the Division on October 19, 1999 and subsequent correspondence dated October 20, 1999 informing Glaxo Wellcome Inc. that the applications were unacceptable for filing. Specifically, it was noted that an appropriate user fee was not received as provided for under Section 736(a)(1)(A)(ii) of the Federal Food, Drug, and Cosmetic Act. The Division stated that the safety data submitted in support of the labeling change were required for approval of the applications. In addition, the Division stated that these supplements will be considered and reviewed as prior approval supplements rather than as a Special Supplement: Changes Being Effected because the changes made to current labeling based on the standard wording provided for in 21 CFR 201.57 (f)(10)(ii)(B) do not add or strengthen PRECAUTIONS, WARNINGS, or CONTRAINDICATIONS and thus do not meet the definition of a Special Supplement: Changes Being Effected as defined in 21 CFR 314.70(c)(2)(i).

The purpose of this correspondence is to respond to the Agency's unacceptability for filing letter for these supplements and to ask you to reconsider the need for a user fee and prior approval based on Agency guidance and recent precedent set by the Agency and your Division for similar applications.

Glaxo Wellcome Inc.

Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

Telephone
919 483 2100

CSO Note:
Internal mtg held 10/29/99 to
discuss this submission. See
mtg. minutes for details.
JWane 11/30/99

GlaxoWellcome

October 21, 1999

NEW CORRESP

ORIGINAL

NC

Russell G. Katz, M.D., Acting Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
HFD-120, WOC2, Room 4049
1451 Rockville Pike
Rockville, MD 20852

CENTER FOR DRUG EVALUATION
AND RESEARCH

OCT 22 1999

RECEIVED HFD-120

Re: NDA 20-241/S-011; LAMICTAL® (lamotrigine) Tablets
NDA 20-764/S-005; LAMICTAL® (lamotrigine) Chewable Dispersible Tablets
General Correspondence: Response to Unacceptability for Filing Letter

Dear Dr. Katz:

Reference is made to the aforementioned applications which were submitted on August 20, 1999 as "Special Supplements: Changes Being Effected" in compliance with the requirements for the *Geriatric Use* subsection of prescription drug labeling as described in 21 CFR 201.57 (f)(10).

Reference is also made to a telephone conversation with the Division on October 19, 1999 and subsequent correspondence dated October 20, 1999 informing Glaxo Wellcome Inc. that the applications were unacceptable for filing. Specifically, it was noted that an appropriate user fee was not received as provided for under Section 736(a)(1)(A)(ii) of the Federal Food, Drug, and Cosmetic Act. The Division stated that the safety data submitted in support of the labeling change were required for approval of the applications. In addition, the Division stated that these supplements will be considered and reviewed as prior approval supplements rather than as a Special Supplement: Changes Being Effected because the changes made to current labeling based on the standard wording provided for in 21 CFR 201.57 (f)(10)(ii)(B) do not add or strengthen PRECAUTIONS, WARNINGS, or CONTRAINDICATIONS and thus do not meet the definition of a Special Supplement: Changes Being Effected as defined in 21 CFR 314.70(c)(2)(i).

The purpose of this correspondence is to respond to the Agency's unacceptability for filing letter for these supplements and to ask you to reconsider the need for a user fee and prior approval based on Agency guidance and recent precedent set by the Agency and your Division for similar applications.

Glaxo Wellcome Inc.

Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

Telephone
919 483 2100

The decision to file these supplements without a user fee was based in large part on the guidance entitled "Content and Format for Geriatric Labeling" which was published in December 1998. Section VII of the guidance states that "supplements that contain clinical data not required for approval because the supplement does not propose to modify statements in the existing approved labeling would generally not be assessed a user fee. For example, most 21 CFR 201.57 (f)(10)(ii)(A) and (B) supplements would not pay a fee." Although this is open to interpretation, we believe that a user fee is not required because we are not proposing any changes other than to add the standard wording provided for under 21 CFR 201.57 (f)(10)(ii)(B).

Another factor in this decision as well as the decision to file these applications under 314.70(c)(2)(i) rather than as prior approval supplements was the fact that a similar "Special Supplement: Changes Being Effected" to comply with the Final Rule on Geriatric Labeling was submitted without a user fee to the Division on August 27, 1998 for WELLBUTRIN (bupropion hydrochloride) Tablets (NDA 18-644/S-016) and incorporated by reference to WELLBUTRIN SR Tablets (NDA 20-358/S-007) and ZYBAN Tablets (NDA20-711/S-004, Division of Anesthetic, Critical Care, and Addiction Drug Products). These supplements were accepted for filing by the Agency, and the supplement for ZYBAN Tablets was approved by the Division of Anesthetic, Critical Care, and Addiction Drug Products on February 24, 1999. The labeling changes based on these supplements have been implemented and are currently in use.

The labeling changes (see attached) in the WELLBUTRIN Tablets submission were very similar to those proposed in the submission for LAMICTAL Tablets. Furthermore, although this supplement was submitted prior to the availability of the guidance document, it contained much of the same information as provided with the supplements for LAMICTAL. Specifically, the submission contained a synopsis of protocol AK1A4003 entitled "A Multicenter, Double-Blind, Randomized Pilot study Comparing the Safety and Efficacy of WELLBUTRIN (bupropion hydrochloride) Sustained Release and Paroxetine in the Treatment of Elderly Outpatients with Moderate to Severe Recurrent Major Depression" which was used in part to support the labeling change; a full report was filed to IND 28,676 (WELLBUTRIN Sustained Release Tablets) on February 26, 1999. This study was similar in objective to Study UK124, which was filed to support similar labeling changes for LAMICTAL Tablets.

In summary, we believe that the Agency's guidance document on Geriatric Labeling Supplements as well as the Division's recent acceptance for filing of a similar application as a "Special Supplement: Changes Being Effected" without the requirement for a user fee supports a similar determination for the above referenced supplements.

Russell G. Katz, M.D.

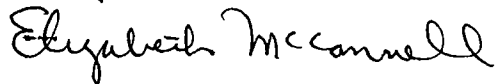
October 21, 1999

Page 3

Thank you for your prompt attention to this matter. We would be available to discuss this further at your convenience.

If you have any questions regarding this submission, please do not hesitate to contact me at 919-483-6466.

Sincerely,

A handwritten signature in cursive script that reads "Elizabeth McConnell".

Elizabeth A. McConnell, Pharm.D.

Project Director

Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
 FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
 Expiration Date: April 30, 2000.
 See OMB Statement on last page.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN
 ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Glaxo Wellcome Inc.		DATE OF SUBMISSION October 21, 1999
TELEPHONE NO. (Include Area Code) (919) 483-2100		FACSIMILE (FAX) Number (Include Area Code) (919) 483-5063
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code and U.S. License number if previously issued): Five Moore Drive Research Triangle Park, NC 27709		AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 20-241		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Lamotrigine	PROPRIETARY NAME (trade name) IF ANY Lamictal® Tablets	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) 3,5-diamino-6-(2,3-dichlorophenyl)-as-triazine	CODE NAME (If any) BW430C	
DOSAGE FORM: Tablets	STRENGTHS: 25mg, 100mg, 150mg, 200mg	ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE
**Adjunctive treatment of partial seizures in pediatrics
 Adjunctive treatment of Lennox Gastaut Syndrome**

APPLICATION INFORMATION

APPLICATION TYPE (check one) NEW DRUG APPLICATION (21 CFR 314.50) ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
 BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE 505 (b) (1) 505 (b) (2) 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
 Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION (check one) ORIGINAL APPLICATION AMENDMENT TO A PENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT SUPAC SUPPLEMENT
 EFFICACY SUPPLEMENT LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

REASON FOR SUBMISSION
Response to Unacceptability for Filing Letter

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (Check all that apply)		
1.	Index	
2.	Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling	
3.	Summary (21 CFR 314.50 (c))	
4.	Chemistry section	
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)	
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
	C. Methods Validation Package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)	
5.	Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2), 21 CFR 601.2)	
6.	Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3), 21 CFR 601.2)	
7.	Clinical Microbiology (21 CFR 314.50 (d) (4))	
8.	Clinical data section (21 CFR 314.50 (d) (5))	
9.	Safety update report (21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)	
10.	Statistical section (21 CFR 314.50 (d) (6), 21 CFR 601.2)	
11.	Case report tabulations (21 CFR 314.50 (f) (1), 21 CFR 601.2)	
12.	Case reports forms (21 CFR 314.50 (f) (2), 21 CFR 601.2)	
13.	Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))	
14.	A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))	
15.	Establishment description (21 CFR Part 600, if applicable)	
16.	Debarment certification (FD&C Act 306 (k)(1))	
17.	Field copy certification (21 CFR 314.5 (K) (3))	
18.	User Fee Cover Sheet (Form FDA 3397)	
X	19. OTHER (Specify) Response to Unacceptability for Filing Letter	
CERTIFICATION		
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:		
<ol style="list-style-type: none"> 1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820. 2. Biological establishment standards in 21 CFR Part 600. 3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809. 4. In the case of a prescription drug or biologic product, prescription drug advertising regulations in 21 CFR 202. 5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99 and 601.12. 6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81. 7. Local, state and Federal environmental impact laws. 		
If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.		
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.		
Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.		
SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Elizabeth A. McConnell, Pharm.D. Project Director, Regulatory Affairs	October 21, 1999
ADDRESS (Street, City, State, and ZIP Code)		Telephone Number
Five Moore Drive Research Triangle Park, NC 27709		(919) 483-6466
Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:		
DHHS, Reports Clearance Officer Paperwork Reduction Project (0910-0338) Hubert H. Humphrey Building, Room 531-H 200 Independence Avenue, S.W. Washington, DC 20201		An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
Please DO NOT RETURN this form to this address.		



61.1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-241/S-011
NDA 20-764/S-005

OCT 20 1999

Glaxo Wellcome Inc.
Attention: Elizabeth A. McConnell, Pharm.D.
Five Moore Drive
Research Triangle Park, NC 27709

Dear Dr. McConnell:

We have received your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Lamictal (lamotrigine) Tablets Lamictal (lamotrigine) Chewable Dispersible Tablets
NDA Number:	20-241 20-764
Supplement Number:	011 005
Date of Applications:	August 20, 1999
Date of Receipt:	August 23, 1999

These supplemental applications propose revised labeling to update the *Geriatric Use* subsection of the current package insert as provided for in 21 CFR 201.57(f)(10).

We have not received the appropriate user fee for these applications. An application is considered incomplete and cannot be accepted for filing until all fees owed have been paid. Therefore, these applications are not accepted for filing. We will not begin a review of these applications' adequacy for filing until FDA has been notified that the appropriate fee has been paid. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 360909
Pittsburgh, PA 15251-6909

NDA 20-241/S-011
NDA 20-764/S-005
Page 2

Checks sent by a courier should be addressed to:

Mellon Bank
Three Mellon Bank Center
27th Floor (FDA 360909)
Pittsburgh, PA 15259-0001

NOTE: This address is for courier delivery only. Make sure the FDA Post Office Box Number (P.O. Box 360909) and the user fee identification number are on the enclosed check.

The receipt date for these submissions (which begins the review for filability) will be the date the review division is notified that payment has been received by the bank.

Additionally, as discussed with you on the telephone, we will review these supplements, once filed, as prior approval supplements rather than as "Special Supplements - Changes Being Effected". Therefore, these supplements will require prior approval from the Agency before implementation.

Please cite the application numbers listed above at the top of the first page of any communications concerning these applications. All communications concerning these supplements should be addressed as follows:

U.S. Postal Service:

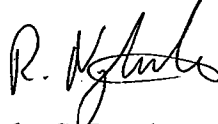
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products
Attention: Document Control Room 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products
Attention: Document Control Room 4008
Woodmont II Bldg, 1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, contact Jacqueline H. Ware, Pharm.D., Project Manager, at 301-594-5793.

Sincerely yours,

 Pur 10/20/99

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation I
Center for Drug Evaluation and Research

NDA 20-241/S-011

NDA 20-764/S-005

Page 3

cc:

Archival NDA 20-241, 20-764

HFD-120 Division file

HFD-120/Ware

HFD-120/Katz/Feeney

HFD-005/Jones/Friedman

Drafted by:jhw/10.19.99

Initialed by:

Final:

filename: C:\My Documents\WPFILES\jwndas\N20241\S011\unltr.doc

UNACCEPTABLE FOR FILING (UN)

APPEARS THIS WAY
ON ORIGINAL



Food and Drug Administration
Rockville MD 20857

NDA 20-241/S-011

SEP 13 1999

Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

Attention: Elizabeth A. McConnell, Pharm.D.
Project Director Regulatory Affairs

Dear Dr. McConnell:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Lamictal (lamotrigine) Tablets

NDA Number: 20-241

Supplement Number: 011

Date of Supplement: 20-Aug-99

Date of Receipt: 23-Aug-99

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on 22-Oct-99 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation I
Attention: Document Control Room 4008
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

Jacqueline H. Ware (JW)
09/10/99

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation I
Center for Drug Evaluation and Research

NDA 20-241/011

Page 2

cc:

Original NDA 20-241/011

HFD-120/Div. Files

HFD-120/CSO/Ware

filename:

SUPPLEMENT ACKNOWLEDGEMENT

APPEARS THIS WAY
ON ORIGINAL

GlaxoWellcome

DUPLICATE

August 28, 2000

CENTER FOR DRUG EVALUATION
AND RESEARCH

AUG 29 2000

RECEIVED HFD-120

Russell G. Katz, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
HFD-120, WOC2, Room 4049
1451 Rockville Pike
Rockville, MD 20852

NEW CORRESP

SEB-011(C)

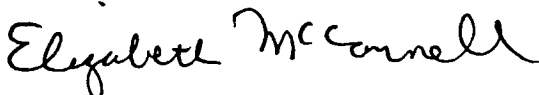
Re: NDA 20-241/S-011; LAMICTAL® (lamotrigine) Tablets
NDA 20-764/S-005; LAMICTAL® (lamotrigine) Chewable Dispersible Tablets
Intent to File Amendment

Dear Dr. Katz:

Reference is made to the Agency's NOT APPROVABLE letter dated August 24, 2000 for the aforementioned applications.

This communication confirms our intent to file an amendment to this application. These include responses to the Agency's comments regarding pharmacokinetics and labeling.

Sincerely,



Elizabeth A. McConnell, Pharm.D.
Project Director
Regulatory Affairs

CSO Note: 9/5/00
Intent Noted.



Glaxo Wellcome Research and Development

Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709-3398

Telephone
919 483 2100

A Division of
Glaxo Wellcome Inc.

GlaxoWellcome

ORIGINAL

August 28, 2000

Russell G. Katz, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
HFD-120, WOC2, Room 4049
1451 Rockville Pike
Rockville, MD 20852

CENTER FOR DRUG EVALUATION
AND RESEARCH

AUG 29 2000

RECEIVED HFD-120

NEW CORRESP
588-011 (C)

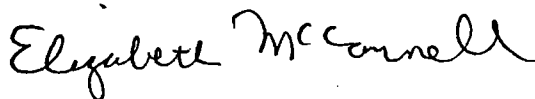
Re: NDA 20-241/S-011; LAMICTAL® (lamotrigine) Tablets
NDA 20-764/S-005; LAMICTAL® (lamotrigine) Chewable Dispersible Tablets
Intent to File Amendment

Dear Dr. Katz:

Reference is made to the Agency's NOT APPROVABLE letter dated August 24, 2000 for the aforementioned applications.

This communication confirms our intent to file an amendment to this application. These include responses to the Agency's comments regarding pharmacokinetics and labeling.

Sincerely,



Elizabeth A. McConnell, Pharm.D.
Project Director
Regulatory Affairs

Glaxo Wellcome Research and Development

Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709-3398

Telephone
919 483 2100

A Division of
Glaxo Wellcome Inc.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338.
Expiration Date: April 30, 2000.
See OMB Statement on last page.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN
ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Glaxo Wellcome Inc.		DATE OF SUBMISSION August 28, 2000	
TELEPHONE NO. (Include Area Code) (919) 483-2100		FACSIMILE (FAX) Number (Include Area Code) (919) 483-5063	
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code and U.S. License number if previously issued): Five Moore Drive Research Triangle Park, NC 27709		AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)		20-241/S-011	
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Lamotrigine		PROPRIETARY NAME (trade name) IF ANY Lamictal® Tablets	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) 3,5-diamino-6-(2,3-dichlorophenyl)-as-triazine		CODE NAME (if any) BW430C	
DOSAGE FORM: Tablets	STRENGTHS: 25mg, 100mg, 150mg, 200mg	ROUTE OF ADMINISTRATION: Oral	

(PROPOSED) INDICATION(S) FOR USE
**Adjunctive treatment of partial seizures in adults and pediatrics
Adjunctive treatment of Lennox Gastaut Syndrome**

APPLICATION INFORMATION

APPLICATION TYPE (check one) NEW DRUG APPLICATION (21 CFR 314.50) ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
 BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE 505 (b) (1) 505 (b) (2) 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION (check one) ORIGINAL APPLICATION AMENDMENT TO A PENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT SUPAC SUPPLEMENT
 EFFICACY SUPPLEMENT LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

REASON FOR SUBMISSION

Intent to File an Amendment

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: <i>(Check all that apply)</i>	
1. Index	
2. Labeling (check one)	<input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
3. Summary (21 CFR 314.50 (c))	
4. Chemistry section	
A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)	
B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
C. Methods Validation Package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)	
5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2), 21 CFR 601.2)	
6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3), 21 CFR 601.2)	
7. Clinical Microbiology (21 CFR 314.50 (d) (4))	
8. Clinical data section (21 CFR 314.50 (d) (5))	
9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)	
10. Statistical section (21 CFR 314.50 (d) (6), 21 CFR 601.2)	
11. Case report tabulations (21 CFR 314.50 (f) (1), 21 CFR 601.2)	
12. Case reports forms (21 CFR 314.50 (f) (2), 21 CFR 601.2)	
13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))	
14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))	
15. Establishment description (21 CFR Part 600, if applicable)	
16. Debarment certification (FD&C Act 306 (k)(1))	
17. Field copy certification (21 CFR 314.5 (K) (3))	
18. User Fee Cover Sheet (Form FDA 3397)	
X	19. OTHER (Specify) Intent to File an Amendment

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biologic product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99 and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Elizabeth A. McConnell, Project Director Regulatory Affairs	DATE August 28, 2000
---	--	--------------------------------

ADDRESS <i>(Street, City, State, and ZIP Code)</i> Five Moore Drive Research Triangle Park, NC 27709	Telephone Number (919) 483-6466
--	---

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

GlaxoWellcome

August 20, 1999

Russell G. Katz, M.D., Acting Director
 Division of Neuropharmacological Drug Products
 Center for Drug Evaluation and Research
 Office of Drug Evaluation I
 Food and Drug Administration
 HFD-120, WOC2, Room 4049
 1451 Rockville Pike
 Rockville, MD 20852

NDA NO. 20-241 REF NO. 3E8-011
 NDA SUPPL FOR Labeling

CENTER FOR DRUG EVALUATION
 AND RESEARCH

AUG 23 1999

ORIGINAL

RECEIVED HFD-120

Re: NDA 20-241; LAMICTAL® (lamotrigine) Tablets
NDA 20-764; LAMICTAL® (lamotrigine) Chewable Dispersible Tablets
Special Supplement: Changes Being Effected, Labeling
Geriatric Labeling Supplement

Dear Dr. Katz:

Reference is made to currently approved NDA 20-241 for LAMICTAL (lamotrigine) Tablets and NDA 20-764 for LAMICTAL (lamotrigine) Chewable Dispersible Tablets.

As provided for in 21 CFR 201.57 (f)(10), we are revising our labeling for the above referenced applications to update the *Geriatric Use* subsection of the current package insert.

Applicable Regulatory Paragraph

The labeling for LAMICTAL is being revised under 21 CFR 201.57 (f)(10)(ii)(B), which provides for standard language for paragraph (ii) labeling if clinical studies included a sufficient number of geriatric subjects to determine whether elderly respond differently and no difference in response was detected.

The original NDA 20-241 included data on 3501 subjects who received LAMICTAL during its clinical development. However, the number of patients age 65 and older who participated in these trials was limited and included approximately 20 patients with epilepsy and 12 healthy elderly subjects who received LAMICTAL as part of a trial comparing the pharmacokinetics of lamotrigine in healthy elderly and young adult volunteers. The results of this clinical pharmacology trial are summarized in the currently approved labeling for LAMICTAL Tablets and LAMICTAL Chewable Dispersible Tablets.

Glaxo Wellcome Research and Development

Five Moore Drive
 PO Box 13398
 Research Triangle Park
 North Carolina 27709

Telephone
 919 483 2100

A Division of
 Glaxo Wellcome Inc.

Russell G. Katz, M.D.

August 20, 1999

Page 2

Glaxo Wellcome recently completed Study UK124, "A Multicenter Double-Blind Randomized Comparative Trial of LAMICTAL and Carbamazepine in Elderly Patients with Newly Diagnosed Epilepsy." This study compared the safety and efficacy of LAMICTAL and carbamazepine in 150 elderly patients (n=102 in the LAMICTAL group and n=48 in the carbamazepine group). Study UK124 was not designed to establish the superiority of LAMICTAL over carbamazepine as monotherapy in elderly patients with epilepsy and as such is not being used to support that indication. However, safety data from this trial form the basis of the integrated safety database of 146 patients which is summarized in this supplement.

The adverse events reported in this cohort of patients did not reveal any differences in the safety profile of LAMICTAL between elderly and younger adult patients (<65 years old). In addition, review of postmarketing reports, epidemiologic data, and published literature did not reveal any information suggesting that elderly subjects respond differently than younger adults to LAMICTAL.

Based on these data, the following revision has been made to the Geriatric Use subsection of the PRECAUTIONS section:



Labeling

The base copy used for this supplement is the labeling provided with the December 14, 1998 approval of LAMICTAL for conversion to monotherapy of partial seizures in adult patients receiving a single enzyme-inducing AED (NDA 20-241/S-003, NDA 20-764/S-001). A "Special Supplement: Changes Being Effected" was subsequently submitted on February 8, 1999 which provided revisions to the CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, OVERDOSAGE, and DOSAGE AND ADMINISTRATION sections.

Included in this supplement is final printed labeling which incorporates the changes made based on the February 8, 1999 submission, as well as those made to the *Geriatric Use* subsection described above. Also included is annotated labeling which shows the revisions to labeling based on the February 8, 1999 submission.

Russell G. Katz, M.D.

August 20, 1999

Page 3

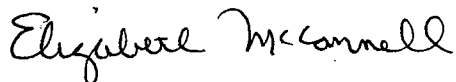
User Fee

Although clinical data are being provided with this submission, Glaxo Wellcome is not proposing any modifications to current labeling other than that provided for in 21 CFR 201.57 (f)(10)(ii)(B). Therefore, no user fee has been submitted for this supplement.

This supplement is being submitted to NDA 20-241, LAMICTAL Tablets and incorporated by reference to NDA 20-764, LAMICTAL Dispersible Tablets.

A desk copy of Volume 1 of this submission is being provided to Jacqueline Ware, Pharm.D., Regulatory Management Officer, under separate cover. If you have any questions regarding this submission, please do not hesitate to contact me at 919-483-6466.

Sincerely,



Elizabeth A. McConnell, Pharm.D.
Project Director
Regulatory Affairs

Cc: Jacqueline Ware, Pharm.D., Regulatory Management Officer, HFD-120 (Volume 1)

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338.
Expiration Date: April 30, 2000.
See OMB Statement on last page.

**APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN
ANTIBIOTIC DRUG FOR HUMAN USE**
(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Glaxo Wellcome Inc.	DATE OF SUBMISSION August 20, 1999
TELEPHONE NO. (Include Area Code) (919) 483-2100	FACSIMILE (FAX) Number (Include Area Code) (919) 483-5063
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code and U.S. License number if previously issued): Five Moore Drive Research Triangle Park, NC 27709	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)		20-241
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Lamotrigine	PROPRIETARY NAME (trade name) IF ANY Lamictal® Tablets	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any) 3,5-diamino-6-(2,3-dichlorophenyl)-as-triazine	CODE NAME (If any) BW430C	
DOSAGE FORM: Tablets	STRENGTHS: 25mg, 100mg, 150mg, 200mg	ROUTE OF ADMINISTRATION: Oral

(PROPOSED) INDICATION(S) FOR USE
**Adjunctive treatment of partial seizures in pediatrics
Adjunctive treatment of Lennox Gastaut Syndrome**

APPLICATION INFORMATION

APPLICATION TYPE (check one) NEW DRUG APPLICATION (21 CFR 314.50) ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
 BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE 505 (b) (1) 505 (b) (2) 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION (check one) ORIGINAL APPLICATION AMENDMENT TO A PENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT SUPAC SUPPLEMENT
 EFFICACY SUPPLEMENT LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

REASON FOR SUBMISSION
Geriatric Labeling Supplement

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 16 THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (Check all that apply)	
X	1. Index
X	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input checked="" type="checkbox"/> Final Printed Labeling
X	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods Validation Package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (21 CFR 314.50 (d) (4))
X	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
X	10. Statistical section (21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (21 CFR 314.50 (f) (1), 21 CFR 601.2)
X	12. Case reports forms (21 CFR 314.50 (f) (2), 21 CFR 601.2)
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
X	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
X	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.5 (K) (3))
X	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION


I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biologic product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99 and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Elizabeth A. McConnell, Pharm.D. Project Director, Regulatory Affairs	DATE August 20, 1999
---	--	--------------------------------

ADDRESS (Street, City, State, and ZIP Code) Five Moore Drive Research Triangle Park, NC 27709	Telephone Number (919) 483-6466
---	---

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.