GlaxoWellcome

October 6, 1998

DESK COPY

Paul D. Leber, 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, Woodmont II, Room 4037
1451 Rockville Pike
Rockville, MD 20852

Re: NDA 20-241/S-003; LAMICTAL® (lamotrigine) Tablets
NDA 20-764/S-001; LAMICTAL® CD (lamotrigine) Chewable Dispersible Tablets
Amendment to Pending Application: Labeling

Dear Dr. Leber:

Reference is made to a teleconference held on October 2, 1998 between members of the Division and Glaxo Wellcome Inc. regarding proposed labeling submitted on April 15, 1998 and September 9, 1998 for the aforementioned applications.

Appended is revised proposed labeling and a rationale for the proposed changes which addresses the Agency's comments from the October 2, 1998 teleconference. The following changes have been made to the proposed labeling:

DOSAGE AND ADMINISTRATION

- Conversion to LAMICTAL monotherapy from an enzyme-inducing AED (EIAED) and from valproate are discussed separately. Recommendations for conversion from an EIAED to LAMICTAL monotherapy are based on the conversion scheme used in the pivotal trial (US 30/31).

- Inclusion of a statement that there is no experience in converting patients from valproic acid to LAMICTAL monotherapy and that no specific guidelines can be offered at this time. The known pharmacokinetic interaction between LAMICTAL and valproic acid are also detailed in this section.

- We propose that the recommendations for initial monotherapy as outlined in the DOSAGE and ADMINISTRTION section remain the same.

Glaxo Wellcome Research and Development
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709
Telephone
919 248 2100
A Division of
Glaxo Wellcome Inc.

INFORMATION FOR THE PATIENT

- Revision of the "How to Use LAMICTAL" section to state that the dose of LAMICTAL should be increased slowly rather than added slowly to reflect patients who may be receiving LAMICTAL as initial monotherapy.

This submission consists of the following:

Attachment 1 contains a rationale for the proposed changes to labeling.

Attachment 2 contains proposed labeling with additions underlined and deletions noted with strike-throughs. The base labeling is that which was submitted to NDA 20-764/S-001 (LAMICTAL Chewable Dispersible Tablets) on September 9, 1998.

Attachment 3 contains a clean, unannotated copy of proposed labeling.

This labeling is being submitted to NDA 20-241/S-003 and incorporated by reference to NDA 20-764/S-001. A desk copy of this submission is being provided to Jacqueline Ware, Pharm.D., Regulatory Management Officer, under separate cover.

Reference is also made to the Agency's request for additional information regarding clinical data from US 17 and US 26, which was submitted in support of the safety of the LAMICTAL 500 mg/day monotherapy dose. A response to this request will be sent under separate cover as soon as the additional information is available.

We are available at your convenience to discuss this submission. If you have any questions regarding this submission, please do not hesitate to contact me at 919-483-6466.

Sincerely,

Elizabeth McConnell

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

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

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	DATE OF SUBMISSION
Glaxo Wellcome Inc.	October 6, 1998
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number *(Include Area Code)***
(919) 483-2100	(919) 483-5063

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code and U.S. License number if previously issued)*:	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Five Moore Drive Research Triangle Park, NC 27709	

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)*	PROPRIETARY NAME (*trade name*) IF ANY
Lamotrigine	Lamictal® Tablets

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME (If any)
3,5-diamino-6-(2,3-dichlorophenyl)-*as*-triazine	BW430C

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	25mg, 100mg, 150mg, 200mg	Oral

(PROPOSED) INDICATION(S) FOR USE

Adjunctive treatment of partial seizures in adults with epilepsy

APPLICATION INFORMATION

APPLICATION TYPE (check one) [X] 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 [X] 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

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

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS [X] 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)	[X] Draft Labeling [ ] 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:

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 McConnell	**Elizabeth A. McConnell, Pharm.D.** **Project Director, Regulatory Affairs**	**October 6, 1998**

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

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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.

FORM FDA 356h (4/97)

NDA 20-241/S-003 LAMICTAL® (lamotrigine) Tablets
NDA 20-764/S-001 LAMICTAL® (lamotrigine) Chewable Dispersible Tablets

Rationale for Proposed Labeling Revisions: Monotherapy

General comments:

- There is a linear relationship between LAMICTAL doses and lamotrigine plasma concentrations.

- The effects of EIAEDs and VPA on LAMICTAL pharmacokinetics are well established.

- A "monotherapy-equivalent dose" is defined as (1) one-half the LAMICTAL dose used with concomitant EIAED or (2) twice the LAMICTAL dose used with concomitant VPA.

- Based on serum concentration data from US 26 and US 17 and dosing data from US 30/31, there is considerable experience at "monotherapy-equivalent" doses of LAMICTAL at 500 mg/day or higher. A total of 503 patients in these two studies received doses $\geq$ 500 mg/day, of which 297 were exposed for at least 6 months, and a total of 306 patients received doses $\geq$ 700 mg/day, of which 197 were exposed for at least 6 months.

- The currently approved LAMICTAL package insert provides for an 8-week titration to "monotherapy-equivalent" doses of 400 mg/day LAMICTAL for patients taking concomitant VPA. Thus, the only gap in direct clinical experience is that between 400 and 500 mg/day.

- The proposed titration rate for escalating initial monotherapy with LAMICTAL from 400 mg/day to 500 mg/day is less than or equal to rates (of predicted serum concentrations) already approved for adjunctive therapy with LAMICTAL and concomitant VPA.

- All of the currently approved dosing schedules use rates that are relatively slow during the first 4-weeks and then allow a slight increase in rate thereafter. None of the proposed monotherapy dosing schedules exceeds the escalation rates associated with currently approved schedules.

- We offer no dosing guidelines for conversion to monotherapy with LAMICTAL in patients receiving more than one concomitant AED.

Rationale for dosing guidelines for "Conversion from a concomitant EIAED to monotherapy with LAMICTAL".

Comment: The Agency expressed a concern about the rate of rise of lamotrigine plasma levels during taper and after discontinuation of the EIAED.

Response: As seen in US 30/31, average plasma concentrations of lamotrigine increased from approximately 4 ug/ml to approximately 8 ug/ml over an 8-week period after the complete withdrawal of the EIAED. This rate of increase (0.5 ug/ml/week) is equal to or less than the rate observed using currently approved dosing guidelines regardless of concomitant AED.

Rationale for dosing guidelines for "Conversion from concomitant VPA to monotherapy with LAMICTAL"

Comment: The Agency expressed a concern about the manner in which under- or over-dosing of LAMICTAL relative to the currently approved dose of LAMICTAL with concomitant VPAcould be avoided following the withdrawal of VPA.

Response: Although the effect of the withdrawal of VPA on lamotrigine serum concentrations is known, the rate at which this effect occurs has not been characterized. As described in the currently approved "Clinical Pharmacology Section", discontinuation of concomitant VPA will result in a halving of lamotrigine plasma concentrations, suggesting a doubling of the LAMICTAL dose would be required to compensate for the loss of VPA's inhibitory effect. We believe it is important to remind the prescribing physician of this pharmacokinetic interaction in the DOSAGE AND ADMINISTRATION section, even though we cannot currently offer specific dosing guidelines for this group of patients.

Rationale for dosing guidelines for "Initial monotherapy in patients > 16 years of age"

Comment: The Agency expressed concerns that the titration phase would be too long if the slowest schedule, that for patients taking concomitant VPA, was used.

Response The proposed dosing schedule for initial monotherapy, which achieves 500 mg/day within 9 weeks, is associated with essentially the same rate of increase in lamotrigine serum concentrations as that seen when the VPA guidelines are used. The safety of the proposed initial monotherapy dosing schedule is based on data in over 400 patients who titrated to a maximum dose of 200 mg/day. Although there are no specific safety data in patients using this titration schedule to achieve monotherapy doses above 200 mg/day, it should be noted that patients taking LAMICTAL 200 mg/day with concomitant VPA in reality experience the pharmacokinetic equivalence of LAMICTAL 400 mg/day as monotherapy. It should be also be noted that these patients have lamotrigine serum concentrations of by Week 6. Thus, the only gap in clinical experience is that between 400 and 500 mg/day. However, since the risk of rash is

greatest in the first 2 to 8 weeks of initiation of LAMICTAL treatment, use of this scheduled is justified.

GlaxoWellcome

July 25, 1997

DESK COPY

Paul D. Leber, 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, Woodmont II, Room 4037
1451 Rockville Pike
Rockville, MD 20852

Re: NDA 20-241; LAMICTAL® (lamotrigine) Tablets
Amendment to Pending Application: Revised Labeling for Supplement 003

Dear Dr. Leber:

Reference is made to correspondence dated December 17, 1996 in which the Agency requested a boxed warning for NDA 20-241, LAMICTAL Tablets, which discusses the risk of serious rash associated with the use of LAMICTAL in adults and children with epilepsy. Wording for the boxed warning and associated changes to the labeling for NDA 20-241 was approved on March 11, 1997.

At this time, we are providing revised labeling for the aforementioned supplemental application (submitted to FDA on February 24, 1997) which incorporates the boxed warning requested by the Agency on December 17, 1996 and approved on March 11, 1997. Differences from the proposed labeling sent with the supplemental application, in particular the change in the proposed minimum age from 13 to 16 years, are specified in the annotated copy. Desk copies of this submission are being provided to John Feeney, M.D., Reviewing Medical Officer, and Jacqueline Ware, Pharm.D., Regulatory Management Officer under separate cover. Diskettes containing an electronic copy of the revised label (unannotated and without revision marks) in Word for Windows format are provided in the archival copy and the desk copies for Drs. Feeney and Ware.

Glaxo Wellcome Research and Development
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

Telephone
919 248 2100

A Division of
Glaxo Wellcome Inc.

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

Sincerely,

Elizabeth McConnell

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

cc: John Feeney, M.D., Reviewing Medical Officer, HFD-120
Jacqueline Ware, Pharm.D., Regulatory Management Officer, HFD-120

APPEARS THIS WAY
ON ORIGINAL

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
July 25, 1997

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)*
6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine

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 with epilepsy

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

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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

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

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	17. Field copy certification (21 CFR 314.5 (K) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

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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.

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Elizabeth McConnell	**Elizabeth A. McConnell, Pharm.D.** **Project Director, Regulatory Affairs**	**July 25, 1997**

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

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

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FORM FDA 356h (4/97)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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

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

OCT 16 1998

Dear Dr. McConnell:

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

We acknowledge receipt of your additional correspondence and amendments to these supplemental applications dated:

NDA 20-241/S-003 only		Both Applications
February 24, 1998	July 16, 1998	October 6, 1998
April 15, 1998	August 21, 1998	October 9, 1998
June 10, 1998	September 9, 1998	
July 2, 1998	October 1, 1998	

The user fee goal date for NDA 20-241/S-003 is October 17, 1998. The user fee goal date for NDA 20-764/S-001 is September 8, 1999.

These supplemental new drug applications are intended to allow for the use of Lamictal (lamotrigine) Tablets and Lamictal (lamotrigine) Chewable Dispersible Tablets as monotherapy for partial seizures in adults with epilepsy.

We have completed the review of these applications, as amended, and have concluded that they are approvable, provided that the products are marketed under labeling that is essentially identical, save for minor editorial changes, to that attached to this letter.

Accordingly, at this time, based on the evidence presented in the applications, we are prepared to approve Lamictal only for use as monotherapy in adult patients already receiving a single EIAED under the conditions of use described in the attached labeling.

Although sections of this proposal are taken verbatim from the labeling proposed by you, other sections have been revised or have been deleted.

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

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

This change may not be implemented until you have been notified in writing that this supplemental application is approved.

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

Sincerely yours,

/S/ 10/16/98

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

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-241/S-003

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

FEB 24 1998

Dear Dr. McConnell:

Please refer to your supplemental new drug application dated February 24, 1997, received February 25, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lamictal (lamotrigine) Tablets, 25mg, 50mg, 100mg, 150mg, 200mg, and 250mg.

We acknowledge receipt of your additional correspondence and amendments to the NDA dated:

June 6, 1997	September 4, 1997	December 16, 1997
July 25, 1997	September 15, 1997	December 23, 1997

The User Fee goal date for this application is February 25, 1998.

This supplemental application provides for the expansion of the indication to include the use of Lamictal as monotherapy of partial seizures in adults with epilepsy.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to respond to the following requests or comments.

Labeling

The attachment to this letter provides a draft of the labeling that the Agency asks you to adopt for Lamictal Tablets upon approval of this application. Although sections of this proposal are taken verbatim from the labeling proposed by you, other sections have been revised. Please note that we have embedded throughout the text of the attached draft labeling, "Notes to Sponsor:", requesting further revisions or clarification of the label.

Please amend your February 24, 1998 response with consolidated labeling which incorporates labeling changes from this letter.

Lastly, to facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

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

Safety Issues

We have a number of requests regarding the presentation of safety data.

1. Sudden Unexplained Deaths

   Please present the data for all Sudden Unexplained Deaths in Epilepsy (SUDEs) with appropriate patient time exposure data for the monotherapy experience. Please express the rate as number of SUDEs/patient-year.

2. Serious Dermatologic Events

   It has been difficult to obtain a clear picture of the number and type of serious rashes that have occurred in this population. Please submit a comprehensive report of all rash, with an emphasis on serious rash; the latter should be defined as had previously been agreed to in our discussions regarding the supplement for Lennox-Gastaut. This report should make clear the incidence of these events for separate cohorts; for patients in the development program, you should make clear which of these patients were still receiving concomitant AEDs and which patients were on true monotherapy. The total exposure under each of these conditions, including patient time, should be presented. Please also submit any post-marketing reports of serious rash in patients receiving monotherapy, with any information about use as monotherapy, if available.

   In addition, for cases seen in the development program, you should present controlled trial data separately from that obtained in open, uncontrolled settings.

3. Other Adverse Events

   We recognize that your draft label presents adverse event data for the Transition Phase and the Monotherapy Phase separately. It has been difficult to find this separate presentation in your NDA. If you have submitted this in your application, please inform us where it is located. If you have not, please submit such a presentation and analysis.

Please understand that the draft labeling may need to be further revised based on your answers to the above comments.

Safety Update

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below:

1. Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted vs now will certainly facilitate review.

2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Provide details of any significant changes or findings, if any.

4. Summarize worldwide experience on the safety of this drug.

5. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

Promotional Material

Please submit three copies of the introductory promotional material that you propose to use for this product. 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 material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

This change may not be implemented until you have been notified in writing that this supplemental application is approved.

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

Sincerely yours,

/S/ — 2/24/98

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