DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-764
NDA 20-241/S-002

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

AUG 24 1998

Dear Dr. McConnell:

Please refer to your new drug application (NDA) dated September 16, 1996, received September 17, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lamictal (lamotrigine) Chewable Dispersible Tablets, 5mg, 25mg, and 100mg.

We also refer to your supplemental new drug application dated September 16, 1996, received September 17, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lamictal (lamotrigine) 25mg, 100mg, 150mg, and 200mg.

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

December 5, 1997	June 4, 1998	July 29, 1998	August 18, 1998
January 15, 1998	June 8, 1998	August 3, 1998 (2)	August 19, 1998 (2)
March 11, 1998	June 23, 1998	August 6, 1998	August 20, 1998
April 20, 1998	June 24, 1998	August 14, 1998	August 21, 1998

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

December 5, 1997	July 29, 1998	August 14, 1998	August 20, 1998
June 23, 1998	August 3, 1998	August 18, 1998	August 21, 1998
June 24, 1998	August 6, 1998	August 19, 1998 (2)	

Your submissions of February 23, 1998 constitute full responses to our December 3, 1997 action letter for these applications. The user fee goal date for these applications is August 24, 1998.

The Lamictal Chewable Dispersible Tablet application provides bioequivalency data to support a new dosage form of lamotrigine, and clinical data to support a new indication for the use of lamotrigine, as compared to the already approved Lamictal Tablet. Specifically, the new indication is for the use of lamotrigine for adjunctive treatment of Lennox-Gastaut syndrome in pediatric and adult patients.

The Lamictal Tablet supplemental application incorporates by reference the clinical data contained in the Lamictal CD Chewable Tablet application so that the approved compressed tablet formulation can gain the new indication, as well. This cross-reference also allows for the development of one label for both lamotrigine products.

We have completed the review of these 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 submitted labeling (package insert dated August 20, 1998, patient package insert dated August 20, 1998, immediate container and carton labels dated June 8, 1998) with the revisions listed below. Accordingly, these applications are approved effective on the date of this letter.

1. The chemical name in the DESCRIPTION section has been changed from "6-(2,3-dichlorphenyl)-1,2,4-triazine-3,5-diamine" to "3,5-diamino-6-(2,3-dichlorophenyl)-*as*-triazine".

2. The following paragraph has been added, as the second paragraph, to the General Dosing Considerations subsection of the DOSAGE AND ADMINISTRATION section:

   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 7 and 8 for patients 2 to 12 years of age, Tables 9 and 10 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.

3. The usual maintenance dose portion of Table 7 has been revised to the following:

   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 5 mg, and add this amount to the previously administered daily dose.

4. The usual maintenance dose portion of Table 8 has been revised to the following:

   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 5 mg, and add this amount to the previously administered daily dose every 1 to 2 weeks.

We note that you have agreed to these revisions as per your August 21, 1998 submission.

These revisions are terms of the NDA and supplemental NDA approval. Marketing these products before making the revisions, exactly as requested, in the products' final printed labeling (FPL) may render the products misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-764 and NDA 20-241/S-002. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of labeling may be required.

Phase 4 Commitments

We remind you of your Phase 4 commitments specified in your submission dated August 19, 1998. These commitments, along with any completion dates agreed upon, are listed below.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Pediatric Exclusivity

We note that your March 11, 1998 submission requests " a determination ... that marketing submissions and approvals for any product containing lamotrigine be subject to the market-exclusivity extension provisions of new section 505A of the Federal Food, Drug, and Cosmetic Act," and specifically refers to two pediatric indications. Lennox-Gastaut syndrome

an[illegible] We have been advised by the CDER Pediatric Exclusivity Implementation Team that the Lennox-Gastaut syndrome data is not eligible for pediatric exclusivity because study reports for the Lennox-Gastaut indication were submitted prior to November 21, 1997.

Other

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product (containers and cartons only) when it is available.

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

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

Sincerely yours

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