# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: 020764 and 020241/S002

## ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

# GlaxoWellcome

August 20, 1998

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 20-764; LAMICTAL® CD (lamotrigine) Chewable Dispersible Tablets**
**NDA 20-241/S-002; LAMICTAL® (lamotrigine) Tablets**
**Amendment to Pending Application: Labeling**

Dear Dr. Leber:

Reference is made to the Agency's facsimile of August 20, 1998 outlining proposed revisions to the labeling for the aforementioned applications which was submitted by Glaxo Wellcome Inc. on August 18, 1998 (and which was revised based on the Agency's comments on August 19, 1998).

Appended is proposed labeling incorporating the Agency's comments from the August 20, 1998 facsimile. Glaxo Wellcome has agreed to all of the Agency's revisions.

This submission consists of the following:

**Attachment 1** contains proposed labeling incorporating the changes as discussed in the August 20, 1998 facsimile. The base label is that submitted on August 18, 1998 incorporating revisions from the Agency's comments on August 19, 1998. Changes to the base label are denoted by underlined text and strike-throughs.

**Attachment 2** contains proposed labeling without revision marks.

**Attachment 3** contains an electronic copy of the proposed revised labeling without revisions in Word 97 format. This is being provided in the archival copy as well as the desk copy for Jacqueline Ware, Pharm.D., Regulatory Management Officer.

This labeling is being submitted to NDA 20-764, LAMICTAL Chewable Dispersible Tablets and incorporated by reference to NDA 20-241/S-002, LAMICTAL Tablets.

**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.

Two desk copies of this submission are being provided to Dr. Ware under separate cover.

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

Sincerely,

Elizabeth McConnell

APPEARS THIS WAY
ON ORIGINAL

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

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

APPEARS THIS WAY
ON ORIGINAL

GlaxoWellcome

August 18, 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 20-764; LAMICTAL® CD (lamotrigine) Chewable Dispersible Tablets**
**NDA 20-241/S-002; LAMICTAL® (lamotrigine) Tablets**
**Amendment to Pending Application: Labeling**

Dear Dr. Leber:

Reference is made to a teleconference held on August 17, 1998 between members of the Division and Glaxo Wellcome Inc. to discuss proposed labeling for the aforementioned applications. The discussion concerned proposed labeling submitted on August 14, 1998 in response to an earlier labeling teleconference held on August 13, 1998.

The Division had the following comments/requests for changes to the proposed labeling:

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This submission consists of the following:

**Attachment 1** contains proposed labeling incorporating the changes as discussed in the August 17, 1998 teleconference. The base label is that submitted on August 14, 1998. Changes to the base label are denoted by underlined text and strike-throughs.

**Attachment 2** contains proposed labeling without revision marks.

This labeling is being submitted to NDA 20-764, LAMICTAL Chewable Dispersible Tablets and incorporated by reference to NDA 20-241/S-002, LAMICTAL Tablets.

Desk copies of this submission are being provided to John Feeney, M.D., Reviewing Medical Officer, and Jacqueline Ware, Pharm.D. under separate cover. Four additional desk copies are being provided to Dr. Ware.

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

Sincerely,

Elizabeth McConnell

APPEARS THIS WAY
ON ORIGINAL

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

Cc: John Feeney, M.D., Reviewing Medical Officer, HFD-120 (via Jacqueline ware, Pharm.D.)
Jacqueline Ware, Pharm.D., Regulatory Management Officer, HFD-120 (5 desk copies)

APPEARS THIS WAY
ON ORIGINAL

# GlaxoWellcome

August 6, 1998

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

APPEARS THIS WAY
ON ORIGINAL

**Re: NDA 20-764; LAMICTAL® CD (lamotrigine) Chewable Dispersible Tablets**
**NDA 20-241/S-002; LAMICTAL® (lamotrigine) Tablets**
**Amendment to Pending Application: Labeling**

APPEARS THIS WAY
ON ORIGINAL

Dear Dr. Leber:

Reference is made to a teleconference held on July 31, 1998 between members of the Division and Glaxo Wellcome Inc. to discuss the proposed labeling submitted on June 24, 1998 in response to the Agency's comments from a previous labeling teleconference held on June 18, 1998.

Appended is proposed labeling incorporating the Agency's comments from the July 31, 1998 teleconference. The majority of the Agency's comments from the teleconference have been incorporated as proposed. Some modifications to the Agency's suggested text are proposed which do not generally alter the intended message.

Specifically, the Agency's proposal for the DOSAGE AND ADMINISTRATION section regarding the use of LAMICTAL in combination with drugs other than enzyme-inducing antiepileptic drugs and valproate has been modified to exclude reference to clonazepam and ethosuximide because of the minimal data available. Rather, we have proposed a more general statement while preserving the concept of using the more conservative dose escalation scheme when LAMICTAL is used in combination with drugs where the pharmacokinetic interaction is unknown.

We have also proposed a modification to the discussion of the time required for pediatric patients to achieve maintenance doses of LAMICTAL (also in the DOSAGE AND ADMINISTRATION section), again to a more general statement that several weeks or months may be required to achieve maintenance, thus allowing for individual variation.

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This change is also reflected in the **Information for the Patient** at the end of the package insert.



This submission consists of the following:

**Attachment 1** contains proposed labeling incorporating the changes as discussed in the July 31, 1998 teleconference. The base label is that submitted on July 29, 1998. Changes to the base label are denoted by underlined text and strike-throughs. Table 4 of the package insert (Treatment-Emergent Adverse Event Incidence in Adults in Placebo-Controlled Adjunctive Trials) has been modified to reflect the Agency's request made in the February 24, 1998 approvable letter for NDA 20-241/S-003 (Adult Monotherapy) to round of the incidence figures to the nearest whole number (a response to this approvable letter was submitted on April 15, 1998).



**Attachment 2** contains proposed labeling without revision marks.

**Attachment 3** contains an electronic copy of the proposed revised labeling without revisions in Word 97 format. This is being provided in the archival copy as well as the desk copy for Jacqueline Ware, Pharm.D., Regulatory Management Officer.

This labeling is being submitted to NDA 20-764, LAMICTAL Chewable Dispersible Tablets and incorporated by reference to NDA 20-241/S-002, LAMICTAL Tablets.

A desk copy of this submission (without an electronic copy of labeling) is also being provided to John Feeney, M.D., Reviewing Medical Officer, under separate cover. Four additional desk copies are being provided to Dr. Ware.

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

Sincerely,

Elizabeth McConnell

APPEARS THIS WAY
ON ORIGINAL

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

Cc: John Feeney, Reviewing Medical Officer, HFD-120 (via Jacqueline Ware, Pharm.D.)
Jacqueline Ware, Pharm.D., Regulatory Management Officer, HFD-120 (5 desk copies)

APPEARS THIS WAY
ON ORIGINAL

# GlaxoWellcome

July 29, 1998

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 20-764; LAMICTAL® CD (lamotrigine) Chewable Dispersible Tablets**
**NDA 20-241/S-002; LAMICTAL® (lamotrigine) Tablets**
**Amendment to Pending Application: Labeling**



Dear Dr. Leber:

Reference is made to a June 18, 1998 teleconference held between members of the Division and Glaxo Wellcome Inc. to discuss our February 23, 1998 response to the Agency's labeling provided with the December 3, 1997 approvable letter for this application. During this teleconference, the Agency requested a further update to the **Acute Multiorgan Failure** subsection of the WARNINGS section, specifically with regard to the rate of death from multiorgan failure in pediatric patients relative to adult patients.



Appended is revised proposed labeling (using our June 24, 1998 submission of LAMICTAL Chewable Dispersible Tablet labeling as the base) incorporating the requested changes. **Attachment 1** contains the proposed labeling with revisions specified by underlining and strike-throughs. **Attachment 2** contains a clean, unannotated version of the proposed labeling.



Please note that the denominator that is used to calculate the relative rates of death from multiorgan failure is limited to the total clinical trial database of 4932 patients (3796 adult patients and 1136 patients) rather than the 7000 patient database described in the current labeling, which includes both clinical trial and compassionate plea/"named" patients. This is because reliable estimates of the total number of participants and the breakdown of adult and pediatric patients in the compassionate plea/"named" patient cohort are not available.

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In the 7000 patient cohort, three adults (two participants in clinical trials and one "named" patient) and two pediatric patients (both participants in clinical trials and described in the original application) died secondary to multiorgan failure. Since submission of NDA 20-764, there has been one additional pediatric death (described in the Final Safety Update for this application which was submitted on February 23, 1998) and no additional adult deaths in clinical trial patients. Thus, the updated rates reflect a total of two adult deaths and three pediatric deaths from multiorgan among the 4932 patients who received LAMICTAL in clinical trials.

Desk copies of this submission are being provided to John Feeney, M.D., Reviewing Medical Officer, Russell Katz, M.D., Deputy Director, and Jacqueline Ware, Pharm.D., Regulatory Management Officer, under separate cover. An electronic copy of the labeling (clean and unannotated) in Word 97 format **(Attachment 3)** is being provided in the archival copy and in the desk copy for Dr. Ware.

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

Sincerely,

Elizabeth McConnell

APPEARS THIS WAY
ON ORIGINAL

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

Cc: John Feeney, M.D., Reviewing Medical Officer, HFD-120 (via Jacqueline Ware, Pharm.D.)
Russell Katz, M.D., Deputy Director, HFD-120 (via Jacqueline Ware, Pharm.D.)
Jacqueline Ware, Pharm.D., Regulatory Management Officer, HFD-120

APPEARS THIS WAY
ON ORIGINAL

GlaxoWellcome

June 24, 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 20-764; LAMICTAL® CD (lamotrigine) Chewable Dispersible Tablets**
**NDA 20-241/S-002; LAMICTAL® (lamotrigine) Tablets**
**Amendment to Pending Application: Labeling**

Dear Dr. Leber:

Reference is made to a teleconference held on June 18, 1998 between members of the Division and Glaxo Wellcome Inc. to discuss the proposed labeling submitted on February 23, 1998 in response to the Agency's December 3, 1997 approvable letter for these applications. Reference is also made to our June 23, 1998 submission of information to support a proposed change to the initial and escalation doses of LAMICTAL in pediatric patients.

APPEARS THIS WAY
ON ORIGINAL

Appended is proposed labeling incorporating the Agency's comments from the June 18, 1998 teleconference as well as the proposed changes to the initial and escalation doses in pediatric patients as presented in the June 23, 1998 submission. The majority of the Agency's comments from the teleconference have been incorporated. However, we are still working to update the **Acute Multiorgan Failure** subsection of the WARNINGS section and will provide that information as soon as it is available.

APPEARS THIS WAY
ON ORIGINAL

This submission consists of the following:

**Attachment 1** contains proposed labeling incorporating the changes as discussed in the June 18, 1998 teleconference. The revision marks note the revisions proposed in our February 23, 1998 response to the Agency's December 3, 1997 approvable letter.

**Attachment 2** contains proposed labeling without revision marks.

**Glaxo Wellcome Research and Development**

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**Attachment 3** contains an electronic copy of the proposed revised labeling without revisions in Word 97 format.

This labeling is being submitted to NDA 20-764, LAMICTAL Chewable Dispersible Tablets and incorporated by reference to NDA 20-241/S-002, LAMICTAL Tablets.

Desk copies of this submission (with an electronic copy of the labeling) are being provided to John Feeney, M.D., Reviewing Medical Officer, and Jacqueline Ware, Pharm.D., Regulatory Management Officer, under separate cover. Four additional desk copies (without an electronic copy of labeling) are also being provided to Dr. Ware.

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

Sincerely,

Elizabeth McConnell

APPEARS THIS WAY
ON ORIGINAL

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

Cc: John Feeney , M.D., Reviewing Medical Officer, HFD-120 (via Jacqueline Ware, Pharm.D.)
Jacqueline Ware, Pharm.D., Regulatory Management Officer, HFD-120 (5 desk copies)

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ON ORIGINAL

**GlaxoWellcome**

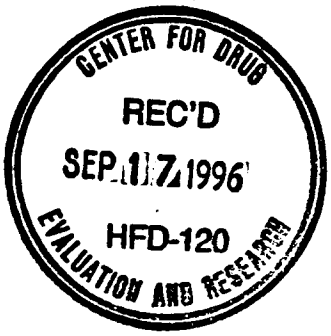
ORIGINAL

NDA NO. 20-241 REF. NO. SE1-002

NDA SUPPL FOR Efficacy 1

September 16, 1996

NDA SUPPLEMENT




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
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1451 Rockville Pike
Rockville, MD 20857

ATTENTION: Paul D. Leber, M.D., Director
Division of Neuropharmacological Drug Products
HFD-120, WOC2, Room 4037

24 Sep 96 See review for NDA 20-764 for comments

**Re: NDA 20-241; LAMICTAL® (lamotrigine) Tablets**
**Supplemental Application: Clinical**
**Additional Clinical Indications**

Dear Dr. Leber:

Pursuant to 21 CFR 314.70 and 21 CFR 314.71, we are submitting a Supplemental Application for LAMICTAL® (lamotrigine) Tablets 25mg, 50mg, 100mg, 150mg, 200mg, and 250mg. The NDA incorporates by reference information contained in NDA 20-764, LAMICTAL CD (lamotrigine) Chewable Dispersible Tablets 5mg, 25mg, 100mg which is being submitted simultaneously with this Supplemental application. NDA 20-764 contains clinical information supporting the use of LAMICTAL for adjunctive treatment of the generalized seizures associated with Lennox-Gastaut syndrome in pediatric and adult patients and for adjunctive treatment of secondarily generalized tonic-clonic seizures in adults with epilepsy. NDA 20-764 also contains data to demonstrate: 1) the bioequivalence of LAMICTAL CD Chewable Dispersible Tablets when given by different routes of administration (chewed, swallowed whole, dispersed in a small volume of liquid); and 2) the bioequivalence of LAMICTAL CD Chewable Dispersible Tablets with the currently marketed LAMICTAL Tablets, NDA 20-241.

**Background/Regulatory History**

LAMICTAL Tablets, a tablet formulation of lamotrigine, was approved on December 27, 1994 (NDA 20-241) and has been marketed in the United States since February 1995 for adjunctive therapy of partial seizures in adults with epilepsy. Seven key placebo-controlled studies were submitted with the original NDA 20-241 as evidence

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that LAMICTAL is effective when used as add-on therapy in treatment-resistant adults with epilepsy. Efficacy data for patients with secondarily generalized tonic-clonic seizures in the original NDA suggested that LAMICTAL was effective in the treatment of these seizures. However, in the Approvable Letter dated July 26, 1994, the Agency indicated there was insufficient evidence to support an efficacy claim for secondarily generalized tonic-clonic seizures at that time. Additional data to support the use of LAMICTAL as adjunctive treatment of secondarily generalized tonic-clonic seizures in adults are presented in the original NDA 20-764 for LAMICTAL CD (lamotrigine) Chewable Dispersible Tablets.

Data from open-label studies in pediatric patients indicating that LAMICTAL was safe and effective as adjunctive treatment of partial were submitted as an amendment to NDA 20-241 (February 16, 1993). Communications with the Agency indicated that data from open-label studies would not be sufficient for approval of LAMICTAL for use in pediatric patients. However, subsequent discussions with the Agency indicated that a single pivotal trial in patients with Lennox-Gastaut syndrome, along with supportive evidence from studies evaluating adjunctive therapy with LAMICTAL in adults with secondarily generalized seizures, would support an indication for LAMICTAL as adjunctive therapy for children and adults with Lennox-Gastaut syndrome.

**Simultaneous Filing of Supplemental NDA to Lamictal Tablets NDA 20-241**

Per previous agreement with the Agency a simultaneous Supplemental NDA for the treatment of Lennox-Gastaut syndrome and secondarily generalized seizures will be submitted to LAMICTAL Tablets, NDA 20-241, incorporating by reference the clinical studies submitted as part of the original NDA for LAMICTAL CD Chewable Dispersible Tablets. It is our understanding that this can be done under the same user fee as the NDA for Lamictal CD Chewable Dispersible Tablets.

It is proposed that one package insert be used for both the Compressed Tablets and the Chewable Dispersible Tablets and that assuming a favorable review, both formulations will have indications for partial seizures with or without secondarily generalized seizures in adults and the generalized seizures associated with Lennox-Gastaut syndrome.

**Contents of the Application**

In addition to the information from NDA 20-241 incorporated by reference, the following additional items are contained in this supplemental application:

- Listing of information incoporated by reference and an overall index to NDA 20-764, LAMICTAL CD (lamotrigine) Chewable Dispersible Tablets.
- Patent information for NDA 20-241, LAMICTAL Tablets.
- Requests for market exclusivity for LAMICTAL Tablets for the proposed indications.
- A supplemental environmental assessment.

We appreciate the Agency's guidance in the submission of this application and look forward to continuing these productive interactions throughout the review of this NDA. During the review process, we will respond promptly and thoroughly to any inquiries. If there are any questions or comments regarding this application, please contact the undersigned at 919-483-6466.

Sincerely,

Elizabeth McConnell

APPEARS THIS WAY
ON ORIGINAL

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

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

APPEARS THIS WAY
ON ORIGINAL

**Memorandum**

**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**

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**DATE:** August 24, 1998

**FROM:** Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

**SUBJECT:** Division Director's Approval Action Memorandum
adjunctive use in Lennox Gastaut
NDA 20-764
&
NDA 20-241/S-002

**TO:** File NDA 20-764, Lamictal (lamotrigine) Chewable Dispersible
File NDA 20-241/S-002 Lamictal (tablets)

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This memorandum records for the administrative file my determination that Burroughs Wellcome's NDA 20-764 for Lamictal Chewable Dispersible tablets and NDA 20-241/S-002 are approved as of this date.

My substantive comments on the evidence bearing on the safety and efficacy of Lamictal as a treatment for Lennox Gastaut were provided in my December 3, 1997 memorandum to the files of these 2 NDAs.

The current regulatory action reflects the review team's conclusion that the sponsor has 1) responded satisfactorily to all requests made in the approvable action letter issued December 3, 1997, and 2) that the information submitted to the file bearing on the safety in use of lamotrigine has not altered the team's prior conclusion that the drug has been shown "safe for use" under the conditions of use recommended in the labeling attached to the approval action letter.

Dr. Russell Katz's supervisory memorandum of 8/19/98 recounts briefly the issues considered and resolved over the interval extending from the issuance of the approvable action to the date of issuance of the approval action. The majority involved labeling development.

Among these, the major clinical/safety issue recognized and resolved

during the post-approvable action period involves the matter of dosing instructions for children.

Lamictal is recommended for use under a regimen that calls for titration from a low initial dose upwards. The absolute dose administered is calculated for individuals based on their body weight. Because the smallest dispersible tablet strength is 5 mg, the required initial starting daily dose and some increments in dose cannot be administered to small body weight children. Although a number of solutions to the problem are possible, it was agreed that either a solution or new solid dosage strengths would be preferred. Until such time that these alternative dosing formulations become available, however, Lamictal will be labeled as unsuitable for use in children below a weight of 17 kilograms. Other sections of labeling were revised to conform to the principle underlying this recommendation (e.g., the rate of dose titration was adjusted to ensure doses were incremented at an appropriate rate).

Another issue of importance is the fact that in the interest of decreasing the incidence of ADRs, the titration schedule recommended in product labeling is less aggressive than that actually evaluated in controlled trials. Were Lamictal intended for use as monotherapy, this approach would be arguable. Given the fact that Lamictal is intended for adjunctive use, however, adoption of a slower rather than a faster titration schedule seems entirely reasonable.



Action Taken

Issuance of an approval action letter.



/S/

Paul Leber, M.D.
8/24/98

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

HFD-101
Temple
HFD-120
Katz
Burkhart
Feeney
WARE

**Memorandum**

**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**

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**DATE:** December 3, 1997

**FROM:** Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

**SUBJECT:** NDA 20-764, Division Director's Approvable Action Memorandum
Lamictal's use in Lennox-Gastaut Syndrome

**TO:** File NDA 20-764, Lamictal (lamotrigine) Chewable Dispersible

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This memorandum records for the administrative file my determination that Burroughs Wellcome's NDA for Lamictal Chewable Dispersible tablets, which provides for the product's use as an adjunctive AED in the management of Lennox Gastaut Syndrome, is approvable.

## Background information about Lamictal

The effectiveness of lamotrigine as an anti-epileptic drug (AED) was established in 3 adequate and well controlled clinical investigations (US 05, US 06 and UK 35) of add-on design. These 3 studies served as the source of substantial evidence that allowed the agency to approve the sponsor's NDA for Lamictal Tablets for adjunctive use in the management of "partial seizures in adults with epilepsy" in 1994.

The present NDA seeks the approval of a new chewable oral formulation of lamotrigine for use in the adjunctive management of a very severe and difficult to control form of childhood onset epilepsy known as the Lennox-Gastaut syndrome. It bears note that the only other AED specifically approved for use in the management of Lennox-Gastaut Syndrome is Felbatol (felbamate), an effective, but very dangerous drug product whose use is associated with a risk of aplastic anemia that is many multiples of the population risk.

**Reciprocal extension of claims based on the Bioequivalence of the Oral Tablet and Oral Chewable Dispersible formulations**

Because the chewable formulation and the tablet formulation (approved under NDA 20-241) of lamotrigine have been shown, on the basis of reports submitted to this NDA, to be bioequivalent (see V.K. Tammara's 5/15/97 biopharm review), the determination that the new chewable formulation is effective in use for the adjunctive management of Lennox-Gastaux syndrome extends to the Tablet formulation. By identical reasoning, the claim (adjunctive use in partial onset seizures in adults) granted the Tablet formulation applies to the chewable dispersible product.

**Safety for Use**

It is self-evident that lamotrigine, given the simple fact that Lamictal Tablets are currently marketed as an adjunctive treatment for seizures of partial onset has, within the meaning of the Act, been deemed to be "safe for use" for that indication. It would ordinarily follow logically, especially in light of the fact that the Lennox-Gastaut Syndrome is acknowledged to be among the more devastating of the epilepsies, that Lamictal is also safe for use for that indication.

There have been concerns, however, about the applicability of this reasoning. They arise because the risk of serious, potentially life-threatening rash (i.e., Stevens Johnson Syndrome[SJS] and toxic epidermal necrolysis[TEN]) is considerably greater (perhaps as much as 10 fold) in children than in adults. Accordingly, because Lennox-Gastaut is basically a condition of childhood, consideration had to be given to the possibility that the benefits associated with the use of Lamictal were insufficient, even in Lennox-Gastaut, to justify its use in patients of pediatric age.

Although the risk of serious rash, once thought to be possibly as high as 1 in 50, did lead some members of the review team to consider recommending a disapproval action, I have long been persuaded, personally, that approval of the NDA, the high incidence of rash notwithstanding, turned primarily on whether or not the evidence supporting Lamictal's use in Lennox-Gastaut was substantial or not. In my

view, even a risk of serious rash as high as the one just cited was fully compatible with approval of the new indication, provided that product labeling carried a clear and prominent warning of that risk. In fact, current Lamictal product labeling already carries a boxed Warning about the risk of serious life-threatening rash and its higher incidence in children.

Despite that view, I had intended until relatively recently to have the NDA presented formally to the PCNS AC so that the evidence and arguments supporting the approvable action in the face of the high risk of serious rash could be thoroughly vetted in a public setting.



Within the past several weeks, however, new information[1] (see Dr. Feeney's November 13, 1997 supplementary clinical review and Dr. Burkhart's 11/18/97 Supervisory Safety Assessment) has become available that has considerably lessened concerns about the both the nature and outcome of what have been identified as "serious" rashes that occur in association with the use of Lamictal. To be fair, the incidence of these rashes remains higher in children, and is not so clearly dose and/or exposure dependent[2] in them as in adults. Moreover, the risk of SJS or TEN in association with Lamictal's use persists, but it now seem reasonable to conclude that Lamictal associated rash, even those cases classified as "serious" rash, run a more benign course than that the review team once feared. Indeed, reviews of individual case reports by expert dermatologists now indicate that many of the cases initially

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[1] Specifically, new reports indicating that the risk of serious rash is probably lower than originally estimated, and, even more critically, in view of advice offered by the agency's expert dermatologists, that a substantive proportion of the "serious" rashes observed are not SJS and do not carry a risk of irreversible injury and death that they had initially been assumed to carry.

[2] In adults, the concomitant use of valproate, increases the risk of serious rash; in children, evidence indicates the risk is not affected by the use of valproate or the dose administered . Importantly, however, the overall risk in children is approximately that seen in adults using valproate as a concomitant AED.

classified as SJS are not SJS at all[3].

Accordingly, in light of this revised view of Lamictal's risks, the indisputably terrible nature of Lennox-Gastaut, and the lack of any fully satisfactory marketed treatments for its managment, I concluded that there was no longer a compelling reason to present the NDA to the PCNS AC.



**Effectiveness for Use.**

**Generic issues concerning reliance on a single study**

The approval of this NDA turns on whether or not there is substantial evidence to support a conclusion that lamotrigine is "effective in use" as an adjunctive treatment for Lennox-Gastaut Syndrome.

Ordinarily, the agency interprets substantial evidence to consist of a body of evidence, adduced in more than one adequate and well controlled clinical investigation, that would allow a fair-minded expert, fully familiar with the clinical management of patients with the disease or condition for which the drug is being evaluated as a treatment, to conclude, fairly and responsibly from the evidence adduced, that the drug has the effect claimed under the conditions of use recommended in its proposed labeling.

In recent years, however, the question of whether or not it is possible for there to be substantial evidence when there are positive results from but one adequate and well controlled clinical investigation has been discussed repeatedly. The question has now been resolved definitively.

Although the ordinary standard for "substantial evidence" of effectiveness has <u>not</u> been modified by the recently enacted FDA Modernization Act of 1997, Section 505 of the Act has been amended to

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[3] See, in particular, the memorandum of 10/21/97 from Dr. Jonathan Wilkin, Director of the Division of Dermatologic and Dental Drug Products and the attached consultative report provided by Ella L. Toombs, M.D.

make explicit the Secretary's authority, "based on relevant science" to conclude that evidence obtained from but a single clinical investigation, taken in association with "confirmatory evidence" from other sources, constitutes substantial evidence of effectiveness.



As the agency's recently promulgated "evidence document" (March 1997) explains, the FDA has long assumed that it has always had this authority, citing numerous examples where the agency has in the past approved a new drug on the basis of a body of evidence that included the affirmative results from but a single adequate and well controlled clinical investigation.



Until new regulations are construed, the 'evidence document' would seem to offer reasonable insight into the nature of the circumstances wherein reliance on the results of a single positive study will ordinarily be acceptable. Accordingly, I have taken the examples offered in that document as guidance. Clearly, the current NDA qualifies in regard to the seriousness of the disease involved and the lack of fully satisfactory alternative treatments for its management. What is potentially arguable is whether the results of the single study reported to the NDA, Study UK 123, provide strong and consistent evidence of Lamictal's effectiveness as an adjunctive treatment for Lennox-Gastaut.



**Does Study UK 123 provide strong and consistent results?**

The background just provided concerning the possibility of a single study serving as a source of substantial evidence has obvious and immediate relevance to the current application because the sponsor has provided the results of but a single adequate and well controlled clinical investigation, Study UK 123, conducted in patients with Lennox-Gastaut to support its claim for the product's effectiveness in that condition.

On initial review, however, Study UK 123 appears to be anything but a strong source of evidence supporting lamotrigine's efficacy in Lennox-Gastaut. To the contrary, the between treatment difference detected by the study's protocol specified primary outcome measure, although favoring Lamictal, fails to attain statistical significance when assessed by the analysis specified as primary by study protocol. Ordinarily, such a

result would bar consideration of the study as a source contributing to the body of substantial evidence, let alone, to be so strong as to stand as the sole controlled clinical study contributing to that requirement.



After extensive and painstaking consideration of the study's results, however, the Division Review team, specifically, Dr. Katz (the team leader) and Dr. Sue-Jane Wang (the consulting biostatistician) have concluded that the failure to attain nominal statistical significance is tantamount to a technical blemish, one arising from the application of an analytical statistical model ill-suited for the kind and source of data generated in this multiclinic study. In fact, a re-analysis of the study's results with methods better suited for the kind and source of the data adduced provides strong and consistent evidence of lamotrigine's effectiveness. (See specifically, TABLE 5R in Dr. Wang's June 26, 1997 review.)



I am persuaded that the review team's interpretation of the study is correct. Given the "technical blemish" just described, however, I do feel obliged to explicate why I am persuaded that Study UK 123 provides strong support for lamotrigine's adjunctive efficacy in the management of Lennox-Gastaut Syndrome.



**My interpretation of Study UK 123**

Study UK 123 is a parallel, placebo controlled, multi-clinic (43 in toto) study of 16 weeks duration, that was conducted with 169 Lennox-Gastaut patients (ages 3-25, but almost 80% of whom were below 12 years of age) randomized to 5 treatment conditions[4] (placebo and 4 different dose levels adjusted for body weight and the use of concomitant valproate).

The 'p' value calculated using the protocol specified analysis (a rank analysis adjusted for center effect) for the realized between group difference (32% vs 9%) in the percent reduction from baseline in the frequency of major seizures [drop attacks and tonic clonic seizures] is 0.069, two tail. As acknowledged, this is a not a statistically significant

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[4] Although randomized to 4 lamotrigine treatment regimens, as specified by protocol, the analysis of the data considered the 4 groups on lamotrigine as one.

result by usual agency test.

The analysis that generated this 'p' value, an extended Mantel-Haenzel Chi Square test employing "standardized midrank scores adjusted for centers," however, is one that can be deemed both ill-suited for this particular clinical trial, and, in my view, perhaps, unnecessarily complicated for the kind of data being analyzed.



First, I rely on Dr. Wang's judgment that the protocol specified analysis, although acceptable enough in theory, is not well suited for the analysis of the data generated in a multiclinic trial where a substantial number of centers do not have patients assigned to each of the treatments being compared. Dr. Wang explains (personal communication) that when it is applied in such circumstances, the analysis, in computing its rank statistic, ignores the response of patients from Centers that have only one of the treatment conditions represented. As a consequence, the protocol specified analysis becomes one that reflects but a subset of the sample of patients randomized. While this may not introduce a systematic bias, it will reduce the study's power to find statistical significance.

This limitation of the primary protocol specified analysis was evidently not considered at the design stage of the trial, presumably because no one involved foresaw the possibility that there would be so many centers with subjects from only one treatment condition. As it turned out (See Table 1 R in Dr. Wang's review), 10 of the 43 planned centers had patients assigned to only one of the two main (lamotrigine and placebo) treatment conditions. Thus, the protocol specified analysis effectively excludes almost 10% of the information generated (14 subjects).

According to Dr. Wang (personal communication), if one wishes, in the face of such "pathology," to retain a "Center" term in a statistical analysis, it is generally deemed prudent to combine the data in such a way as to ensure that every center has at least one patient from each treatment.

When Dr. Wang performed such a maneuver and compared the results for the same analytical approach[5] applied to the data identified as to its

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[5] an aligned rank test-see pages 13 and 14 of her June 26, 1997 review)

actual center of origin with one applied to the data as if the latter had been collected from "centers" based on "region" [i.e. country], she found a dramatic difference supporting her conjecture about the importance of the Center term. The analysis of the data identified as to its actual center of origin generated a 'p' value of 0.042; an analysis of the same data identified as arising from a set of centers (i.e, characterized as "regions," each of which now contained patients from both treatment conditions), produced a 'p' value of 0.003. Thus, Dr. Wang's exploratory analyses effectively establish that the level of computed statistical significance for Study UK 123's findings is hostage to the choice of an analytical model and, in particular, to the way in which the primary analysis deals with Centers at which there are an incomplete representation of the investigational treatments.



It seems to me that a decision on the effectiveness of a drug product cannot logically be allowed to turn on such a technical and arcane matter. Indeed, the strong effect of Center in this situation raises for me the more general question of whether or not it is sensible to include, virtually as a matter of routine, Center and Center by Treatment interaction terms in models for the analysis of all clinical trials. There may be instances when a model without a Center term is fully appropriate, especially if the inclusion of the Center term seems likely to complicate, as it did in this case, the subsequent analysis of the study.[6]



I am mindful, of course, that Center and Center by Treatment terms may be especially important in settings where there is concern about the consistency of treatment effects among centers (e.g., when questions about fraud arise) or when the assessment of outcome may vary considerably as a function of Center. The potential for Centers to vary in regard to patient selection and outcome analysis in a test of an

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[6] For example, in the study of a treatment for a rare orphan indication, it may be important to include a large number of investigators/centers in a study so as to ensure an adequate number of patients. It is likely in such circumstances that a good number of participating investigators, their good intentions notwithstanding, will fail to enter their quota of subjects. In such circumstances, it might make sense to avoid an analysis that excludes patients from centers failing to contain subjects assigned to all treatments, or one that reduces overall efficiency in order to assess the importance of Centers and Center by treatment interaction.

antidepressant seems self-evident. Whether or not Center effects are as important in a study of a stereotypic condition like Lennox-Gastaut where counts of seizures is the outcome measure is far less clear.



In particular, had the protocol specified primary analysis of UK 123 called for an examination of seizure frequency without reference to Center, I would have in all likelihood found it acceptable. To be clear, I would still have been interested in an accounting of the results by Center (as part of the review process), but that is not the same as demanding that Center be included as a term in the primary data analysis intended to assess whether or not the drug was effective. Thus, it is of considerable importance to me that when Dr. Wang conducted an analysis of the ranks of percent change from baseline for Lamictal and placebo, ignoring Center entirely, she obtained a highly significant between treatment difference (p=0.003). I find in this simple analysis of the data very strong support for the conclusion that lamotrigine suppresses the frequency of major seizures in patients with Lennox-Gastaut.



I am mindful that the approach taken here may seem, at least insofar as it can be described as data conditioned and ad hoc, to be equivalent to the very approach the agency regularly faults when it is undertaken by sponsors seeking to find support for their claims in re-analyses of clinical trials that have failed to generate a positive result under their protocol designated analyses. There are, I would acknowledge, similarities, but I would also argue they are entirely superficial.

To begin, the agency's intent in carrying out its post hoc analyses was not to find a favorable result, per se, but to obtain a fair and reasonable estimate of how likely it is that the differences observed in Study UK 123 were due to an effect of lamotrigine rather than to the operation of chance. The Team's efforts were driven by an appreciation of the fact that the study, as conducted, had generated a distribution of patients and centers that was not well suited (in regard to its form) to analysis by the study's protocol specified analysis.

Secondly, the ad hoc analyses conducted by the Review Team are less complex than that proposed in the protocol of Study UK 123. By principle of parsimony, (i.e, by test of Occam's razor), the results of a simple

analysis are typically afforded greater weight than those generated by a more complex model. Indeed, to the extent that post hoc analyses are ever allowable, it can be argued that one which make no adjustments whatsoever differs intrinsically from any and all that rely on a de novo model, the terms of which are specified only after an exhaustive review of the evidence adduced.



In sum, I am persuaded that Study UK 123, the results of its protocol specified analysis notwithstanding, is a study that provides strong and unambiguous support for the conclusion that lamotrigine, in adjunctive use, can reduce the frequency of major seizures in patients with Lennox-Gastaut Syndrome.



**Is there substantial evidence of Lamictal's effectiveness in use as an adjunctive treatment for Lennox-Gastaut Syndrome?**

Upon review of the arguments made by the review team, (see in particular, Dr. Katz's 11/17/97 memorandum), I am persuaded that the evidence, including in particular the strong results of study UK 123, constitutes substantial evidence of lamotrigine's effectiveness as an adjunctive treatment for Lennox-Gastaut Syndrome.



This conclusion notwithstanding, it would still be preferable to have had access to the results of additional clinical investigations in patients with Lennox-Gastaut providing fully independent substantiation. In any case, I am persuaded that an expert fully familiar with the management of patients with Lennox-Gastaut syndrome could fairly and responsibly conclude, based on the results of the single adequate and well controlled clinical investigation submitted (UK 123), results un-rebutted by contradictory findings from other adequate and well controlled clinical investigations, that Lamictal is effective in adjunctive use as an AED for treatment of the Lennox-Gastaut Syndrome.

**Some caveats about the basis for this determination**

The determination that there is substantial evidence of Lamictal's effectiveness in the management of Lennox-Gastaut should not be taken as a precedent that a single study can invariably provide substantial evidence

for a new claimed use of an already marketed AED.

A distinction must be drawn between circumstances in which there is but one RCT and it is determined to have a positive result, and those in which there are several adequate and well controlled investigations, but only one among them is positive. In the face of conflicting study results, prudence would demand that effectiveness be supported by positive results from more than a single experiment.



Also of importance to a determination that there is substantial evidence is the existence of positive evidence from other controlled clinical trials that may be deemed to provide (via extrapolation) some collateral support for the new claim. In the case of Lamictal, the existence of a number of controlled clinical trials persuasively documenting that lamotrigine is effective in adjunctive use as an AED against partial onset seizures was only of arguable importance, however, because Lennox-Gastaut is a syndrome comprised of a variety of generalized seizures.



**Labeling**

Currently approved Lamictal Tablet product labeling not only carries a boxed Warning about the risks of serious rash associated with the product's use, but makes clear that the risk is considerably increased in children as compared to adults. Accordingly, the major task vis a vis product labeling associated with this approvable action has entailed revisions to approved Lamictal labeling.

Upon review, I am persuaded that the draft of labeling attached to the approvable action letter forwarded for my signature provides, with minor modification, labeling that fully and accurately depicts the benefits and risks associated with the use of Lamictal as an adjunctive treatment for the management of Lennox-Gastaut.



**Miscellaneous issues**

A number of technical and routine matters require resolution prior to final approval of the application. These range from minor changes to the name

of the product to the submission of the required safety update. None require additional comment.

APPEARS THIS WAY
ON ORIGINAL

**Action Taken**

Issuance of an approvable action letter on NDA 20-764 (and approval of supplement S-002 to NDA 20-241)

/S/

Paul Leber, M.D.
12/3/97

APPEARS THIS WAY
ON ORIGINAL

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

HFD-101
Temple
HFD-120
Katz
Burkhart
Feeney
Tresely
Fitzgerald
Aisar
Guzewska
WARE
HFD-710
Wang
Sahlroot
HFD-860
Sahajwallah
Tammara