

Exclusivity Summary Form

EXCLUSIVITY SUMMARY FOR NDA # 20-241

SUPPL # S-002

Trade Name: Lamictal (lamotrigine) Tablets

Generic Name: lamotrigine

Applicant Name: Glaxo Wellcome

HFD#: HFD-120

Approval Date If Known: 8-24-98

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 question about the submission.

a) Is it an original NDA?

YES/ / NO / /

b) Is it an effectiveness supplement?

YES / / NO / /

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

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / / NO / /

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

The applicant has requested 3 years of exclusivity from the date of approval.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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 8.

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 8 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES.

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-241: Lamictal (lamotrigine)Tablets

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# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. 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 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / / NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / / NO / /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / / NO / /

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / / NO / /

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES / / NO / /

Investigation #2 YES / / NO / /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES / / NO / /

Investigation #2 YES / / NO / /

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

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study UK 123 _____

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?

N/A

Investigation #1

YES / ___ / Explain _____ NO / ___ / Explain _____

APPEARS THIS WAY
ON ORIGINAL

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: _____

NDA 20-764

Lamictal® CD (lamotrigine) Chewable Dispersible Tablets 5 mg, 25mg, 100mg

Request for Marketing Exclusivity

Pursuant to Sections 505(c)(3)(D)(iv) and 505(j)(4)(D)(iv) of the Federal Food, Drug, and Cosmetic Act and 21CFR 314.108(b)(4), Glaxo Wellcome Inc. requests three years of exclusivity from the date of approval of Lamictal® CD (lamotrigine) Chewable Dispersible Tablets 5mg, 25mg, 100mg for the adjunctive treatment of generalized seizures associated with Lennox-Gastaut syndrome in pediatric and adult patients.

We hereby certify to the following:

Item 8, Section 5.4.19 of this application contains a list of published studies or publicly available reports of clinical investigations known to Glaxo Wellcome through a literature search that are relevant to the use of Lamictal for treatment of Lennox-Gastaut syndrome. Glaxo Wellcome has thoroughly searched the literature and to the best of our knowledge, the list is complete and accurate and, in our opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of Lamictal for such use.

Thus, Glaxo Wellcome Inc. is entitled to exclusivity as this application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and sponsored by Glaxo Wellcome Inc. The following investigation is "essential to the approval of the application" in that there are no other data available that could support FDA approval of the application:

Study H34-123-C93 Lamotrigine as Add-on Therapy in Patients with a Clinical Diagnosis of a Lennox-Gastaut Syndrome (Severe Generalized Epilepsy of Childhood Onset). A Multicentre, Double-blind, Placebo-controlled, Parallel Group Study

The clinical investigation is defined as "new" as it has not been relied on by the FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and does not duplicate the results of another investigation that was relied on by FDA to demonstrate the effectiveness or safety in a new patient population of a previously approved drug application.

This investigation was "conducted or sponsored by Glaxo Wellcome" in that Glaxo Wellcome Inc. was the sponsor of the investigational new drug application (IND 43,551) under which the investigation essential to approval of the application was conducted.

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

9/5/96
Date

APPEARS THIS WAY
ON ORIGINAL

NDA 20-241

Lamictal® (lamotrigine) Tablets 25mg, 50mg, 100mg, 150mg, 200mg,250mg

Request for Marketing Exclusivity

Pursuant to Sections 505(c)(3)(D)(iv) and 505(j)(4)(D)(iv) of the Federal Food, Drug, and Cosmetic Act and 21CFR 314.108(b)(5), Glaxo Wellcome Inc. requests three years of exclusivity from the date of approval of Lamictal® (lamotrigine) Tablets 25mg, 50mg, 100mg, 150mg, 200mg,250mg for the adjunctive treatment of generalized seizures associated with Lennox-Gastaut syndrome in pediatric and adult patients.

We hereby certify to the following:

Item 8, Section 5.4.19 of NDA 20-764, (LAMICTAL CD (lamotrigine) Chewable Dispersible Tablets 5mg, 25mg, 100mg) , incorporated by reference to this application, contains a list of published studies or publicly available reports of clinical investigations known to Glaxo Wellcome through a literature search that are relevant to the use of Lamictal for treatment of Lennox-Gastaut syndrome. Glaxo Wellcome has thoroughly searched the literature and to the best of our knowledge, the list is complete and accurate and, in our opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of Lamictal for such use.

Thus, Glaxo Wellcome Inc. is entitled to exclusivity as this application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and sponsored by Glaxo Wellcome Inc. The following investigation is "essential to the approval of the application" in that there are no other data available that could support FDA approval of the application:

Study H34-123-C93 Lamotrigine as Add-on Therapy in Patients with a Clinical Diagnosis of a Lennox-Gastaut Syndrome (Severe Generalized Epilepsy of Childhood Onset). A Multicentre, Double-blind, Placebo-controlled, Parallel Group Study

The clinical investigation is defined as "new" as it has not been relied on by the FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and does not duplicate the results of another investigation that was relied on by FDA to demonstrate the effectiveness or safety in a new patient population of a previously approved drug application.

This investigation was "conducted or sponsored by Glaxo Wellcome" in that Glaxo Wellcome Inc. was the sponsor of the investigational new drug application (IND 43,551) under which the investigation essential to approval of the application was conducted.

APPEARS THIS WAY
ON ORIGINAL

Elizabeth McConnell

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

9/16/96

Date

APPEARS THIS WAY
ON ORIGINAL

GlaxoWellcome

DUPLICATE

June 4, 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

CENTER FOR DRUG EVALUATION
AND RESEARCH **2012 AMENDMENT**

JUN 05 1998

N(XR)

RECEIVED HFD-120

Re: NDA 20-764; LAMICTAL® CD (lamotrigine) Chewable Dispersible Tablets
General Correspondence: Market Exclusivity

Dear Dr. Leber:

Reference is made to the aforementioned application submitted to FDA on September 16, 1996 and to the request for market exclusivity provided with the application (Volume 1, page xix). Glaxo Wellcome Inc. had requested three years of market exclusivity for the use of LAMICTAL as adjunctive treatment for pediatric and adult patients with Lennox-Gastaut syndrome.

We also wish to note that on August 23, 1995, Glaxo Wellcome Inc. received an orphan designation for the use of LAMICTAL for this disorder. A copy of correspondence granting this designation is appended (**Attachment 1**). Under the provisions of the Orphan Drug Act, Glaxo Wellcome Inc. would thereafter also be eligible for seven years of market exclusivity for the use of LAMICTAL for treatment of Lennox-Gastaut syndrome upon approval of this application.

The purpose of this correspondence is to clarify that our request for three years of market exclusivity provided with our original application is not intended to supercede or diminish the seven years of exclusivity for which we are also eligible under our orphan drug designation with the orphan designation granted for LAMICTAL for this indication. Glaxo Wellcome Inc. intends to file a request for a period of seven years of marketing exclusivity under the Orphan Drug Act upon the approval of LAMICTAL for treatment of Lennox-Gastaut syndrome. A statement notifying the Agency of our intent to file this request is appended (**Attachment 2**).

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.

Paul D. Leber, M.D.

June 4, 1998

Page 2

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

APPEARS THIS WAY
ON ORIGINAL

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

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA # 20-764

HFD-120

Trade (generic) name/dosage form: Lamictal CD (lamotrigine) Chewable Dispersible Tablets

NDA # 20-241 Supplement # 002 Circle one: SE1, SE2, SE3, SE4, SE5, SE6

Trade (generic) name/dosage form: Lamictal (lamotrigine) Tablets

Action: AP AE NA

Applicant Glaxo Wellcome

Therapeutic Class 3S

Indication(s) previously approved: adjunctive therapy of partial seizures in adults

Pediatric labeling of approved indication(s) is adequate inadequate

Indication in this application: adjunctive treatment of Lennox-Gastaut syndrome in pediatric and adult patients

(For supplements, answer the following questions in relation to the proposed indication.)

1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.
2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.
- a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- b. The applicant has committed to doing such studies as will be required.
- (1) Studies are ongoing.
- (2) Protocols were submitted and approved.
- (3) Protocols were submitted and are under review.
- (4) If no protocol has been submitted, explain the status of discussions on the back of this form.
- c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.
4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

/S/
Signature of Preparer and Title (PM, CSO, MD, other) Project Manager Date 8/24/98

cc: Orig NDA
HFD-120/Div File
NDA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

Lamictal® (lamotrigine) CD Chewable Dispersible Tablets

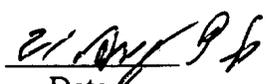
NDA 20-764

DEBARMENT CERTIFICATION

Glaxo Wellcome hereby certifies that to the best of its knowledge and belief, it did not and will not use in any capacity the services of any person debarred under section 306(a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application.

APPEARS THIS CERTIFICATE
ON FILE


Richard Kiernan
Worldwide Director, GLP and GCP Compliance


Date

APPEARS THIS CERTIFICATE
ON FILE

REQUEST FOR PROPRIETARY/ESTABLISHED NAME REVIEW

To: CDER Labeling and Nomenclature Committee
Attention: Dan Boring, R.Ph., Ph.D., Chair
HFD-530
9201 Corporate Blvd, Room N461

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

Date: September 18, 1997

Application Status (IND/NDA/ANDA): NDA 20-764

Proposed Proprietary Name: Lamictal CD Chewable Dispersible Tablets

Trademark registration status/Countries registered(if known): Registered
Company tradename: GlaxoWellcome

Other proprietary names by same firm for companion products: Lamictal Tablets

United States Adopted Name, dosage form:
lamotrigine chewable dispersible tablets

Indication for use: Lamictal is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalization and as adjunctive therapy in the generalized seizures of Lennox-Gastaut syndrome in pediatric and adult patients.

Comments from submitter (concerns, observations, etc.):

NOTE: Please review Glaxo's response to the LNC recommendation from 11/18/96 (See attachment) of this proposed Trademark. We would appreciate the committee's response to this consult by November 1, 1997 in order that we might have sufficient lead time to consider your recommendation and meet our user fee due dates.

Thank you in advance for your assistance in this matter.

Meetings of the Committee are scheduled for the 4th Tuesday of each month. Please submit this form at least one week before the meeting. Responses will be as timely as possible.

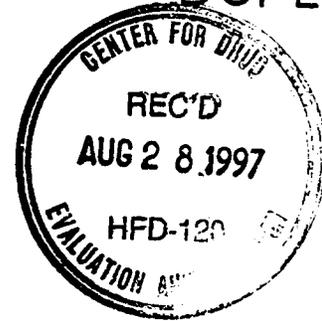
Rev. 2/97

cc
NDA 20-764
HFD-120/Division File
HFD-120/CSO/JWare/Guzewska/Blum

GlaxoWellcome

DUPLICATE

August 27, 1997



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

NEW CORRESP.

**Re: NDA 20-764; LAMICTAL® CD (lamotrigine) Chewable Dispersible Tablets
Amendment to Pending Application
Response to FDA Request/Comment: Proposed Proprietary Name**

Dear Dr. Leber:

APPEARS THIS WAY
ON ORIGINAL

Reference is made to comments received on November 22, 1996 from the FDA's Labeling and Nomenclature Committee (LNC) regarding the acceptability of the proposed proprietary name for the aforementioned application. The LNC stated several objections to the proposed name.

The purpose of this correspondence is to respond to the LNC's comments and request that the Agency accept LAMICTAL CD (lamotrigine) Chewable Dispersible Tablets as the official name for this product. Appended are the LNC's comments (in bold print) and our responses to these comments.

We would appreciate the Agency's consideration of our response on this matter at your earliest convenience.

APPEARS THIS WAY
ON ORIGINAL

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.

Paul D. Leber, M.D.
August 27, 1997
Page 2

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

NDA 20-764
LAMICTAL® CD (lamotrigine) Chewable Dispersible Tablets

**Response to Labeling and Nomenclature Committee (LNC) Comments Regarding
the Acceptability of the Proposed Proprietary Name**

**The abbreviation CD is inappropriate since CD is already in use to mean
"Controlled Dose", a description of a controlled release product.**

Glaxo Wellcome shares the LNC's interest in avoiding the risk of confusion on behalf of patients and healthcare providers; however, after careful consideration, we are confident that there is no such risk presented by the use of "CD" in the proprietary name for LAMICTAL and that it is unlikely that healthcare providers and patients would interpret CD as "controlled dose" or extended release form of LAMICTAL.

Patients with epilepsy are likely to exercise a great deal of caution in taking their epilepsy medications, in light of the important role that these medicines play in the lives of these patients. We submit that it is unlikely that a doctor or a patient with epilepsy would disregard specific dosing instructions provided with LAMICTAL in favor of a general impression derived from one interpretation of the suffix "CD", particularly since the term "Chewable Dispersible" follows this suffix in the proprietary name. Furthermore, there are benefits in communicating to the patient the different options for administration (e.g., chewing, swallowing whole, or dispersing in liquid). Such communication will likely lead to additional discussions regarding the possible benefits and/or side effects of LAMICTAL, as well as directions reinforcing the importance of following dosing instructions closely. This will likely result in maximizing the benefits of LAMICTAL while minimizing possible side effects.

Although Glaxo Wellcome acknowledges that "CD" could be used as an abbreviation for "controlled dose", this abbreviation has other meanings as well. For example, the 1992 edition of Stedman's Medical Acronyms lists more than 50 meanings for the acronym "CD", including "cardiac disease," "cardiac dysrhythmia," "celiac disease", "chemical dependency," "combination drug," "convulsive disorder," "convulsive dose", and "curative dose". In light of these numerous other meanings for "CD", and the further clarification of "Chewable Dispersible" in the product name, we submit that there is no commonly understood meaning for this designation and that patients and healthcare providers are therefore unlikely to automatically interpret the designation as referring to "controlled dose".

Paul D. Leber, M.D.
August 27, 1997
Page 4

The descriptive nomenclature "Chewable Dispersible" appears redundant and the use of "Dispersible" is not recommended.

The established name should be (lamotrigine tablets) chewable. USP does not specifically recognize the term "dispersible" and to be in conformance with USP established name conventions, it should not appear in a USP title.

The designation "Chewable Dispersible" is intended to convey two separate options for administration of this product and in our opinion is not redundant. Glaxo Wellcome Inc. has conducted several studies demonstrating the bioavailability of this formulation when chewed, swallowed whole, or dispersed in liquid; furthermore, patients participating in the pivotal clinical trial contained in NDA 20-764 (UK 123) had these administration options.

In addition, there is a product that is currently marketed that carries the "Chewable Dispersible" designation; that is VIDEX[®] (didanosine) Chewable Dispersible Buffered Tablets (Bristol-Myers Squibb), which has been approved since October 1991. Furthermore, VIDEX carries the designation "dispersible" in its official name despite the lack of a USP standard.

Although there is no USP standard for dispersible tablets, the British Pharmacopoeia (BP) defines Dispersible tablets as "uncoated tablets that produce a uniform dispersion in water. The BP provides specific criteria for Disintegration, Uniformity of Dispersion, and Uniformity of Weight that are applicable to dispersible tablet formulations. LAMICTAL CD (lamotrigine) Chewable Dispersible Tablets comply with BP criteria for Uniformity of Dispersion applicable to a dispersible tablet formulation. Content Uniformity testing is performed in lieu of Uniformity of Weight. Dissolution testing is performed in lieu of Disintegration.

Thus, the term "dispersible" is a pharmaceutically recognized term with defined criteria and standards and provides a description of an alternative method of administration distinct from "chewable" alone.

Paul D. Leber, M.D.

August 27, 1997

Page 5

Summary

Glaxo Wellcome respectfully requests that the Agency accept LAMICTAL® (lamotrigine) CD Chewable Dispersible Tablets as the proprietary name for this product for the following reasons:

- We submit that it is unlikely that a doctor or a patient with epilepsy would disregard specific dosing instructions provided with this medicine in favor of a general impression derived from one interpretation of the suffix "CD", particularly since the term "Chewable Dispersible" follows this suffix in the proprietary name. Furthermore, by communicating the different options of administration as defined by the "CD" suffix will likely lead to further discussions regarding possible benefits and risks of LAMICTAL, as well as reinforcement of the importance of following dosage instructions closely. This would result in maximizing the potential benefits of LAMICTAL while decreasing the risk of side effects.
- Although it is possible that "CD" implies "controlled dose", there are multiple other meanings for this abbreviation. In light of these numerous other meanings for "CD", and the further clarification of "Chewable Dispersible" in the product name, we submit that there is no commonly understood meaning for this designation and that patients and healthcare providers are therefore unlikely to automatically interpret the designation as referring to "controlled dose".
- There is a currently marketed product with the "Chewable Dispersible" designation (VIDEX® [didanosine] Chewable Dispersible Buffered Tablets).
- Although there is not a USP standard for dispersible tablets, LAMICTAL CD Chewable Dispersible Tablets comply with criteria for dispersible tablets as defined in the British Pharmacopoeia.

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM OF TELEPHONE CONVERSATION

Date 11/22/96
INDANDA N20-764
Sponsor Glaxo
Drug Lamotrigine Chewable Dispersible tablet
Phone 919-483-6466
Contact Betty McConnell
Subject **Comments from Nomenclature Committee**

APPEARS THIS WAY
ON ORIGINAL

Summary:

At the request of Dr. Katz, I contacted Dr. McConnell and informed her of comments from the Agency's Nomenclature Committee regarding her firm's product (Lamictal CD). The committee found both the established name and the proposed proprietary name for this product to be unacceptable. The committee's specific comments were also relayed to the firm via fax (see attachment).

Dr. McConnell expressed her understanding and appreciation of this feedback.

Jackie Ware, Pharm.D.
Project Manager

cc: APPEARS THIS WAY
ORIG ON ORIGINAL
HFD-120
HFD-120/Leber/Katz/Feeney/Tresley
HFD-120/Blum/Guzewska/Ware
Doc: filemaker pro

/S/

APPEARS THIS WAY
ON ORIGINAL

Consult #688 (HFD-120)

Lamictal CD Chewable Dispersible Tablets

lamotrigine chewable dispersible
tablets

There were no look-alike/sound-alike conflicts or misleading aspects noted with the proposed proprietary name. However, the Committee feels that the abbreviation CD is inappropriate since CD is already in use to mean "Controlled Dose", a description of a controlled release product. The descriptive nomenclature "Chewable Dispersible" appears redundant and the use of "Dispersible" is not recommended.

The Committee further believes that the established name for this product should be (lamotrigine tablets) chewable. The USP does not specifically recognize the term "dispersible" and to be in conformance with the USP established name conventions, it should not appear in a USP title.

The Committee finds the proposed proprietary and established names to be unacceptable.

IS/ 11/18/96, Chair
CDER Labeling and Nomenclature Committee

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

RECEIVED NOV 17 1997

Date: October 21, 1997

From: Director
Division of Dermatologic and Dental Drug Products,
HFD-540

Subject: Division Director's Memorandum to Consult report on
lamotrigine rashes by MO, signed October 8, 1997,
(requested on August 26, 1997, delivered on
September 26, 1997).

To: Dr. John J. Feeney, III
Division of Neuropharmacological Drug Products
Through: Director, Office of Drug Evaluation V,
HFD-105 /S/ 10/22/97
Director, Office of Drug Evaluation I,
HFD-101 /S/ 10/31/97
Director, Office of Neuropharmacological
Drug Products, HFD-120 /S/ 11/3/97

The term Stevens-Johnson syndrome is a frequently used synonym for erythema multiforme major, resulting in confusion. The two are different conditions that are usually clinically distinguishable. Patients with erythema multiforme major have typical target lesions, predominantly on the extremities. Erythema multiforme major usually occurs after infections especially herpes simplex and mycoplasma, and has a benign course. Patients with widely distributed purpuric macules and blisters and prominent involvement of the trunk and face are likely to have Stevens-Johnson syndrome, which is usually drug-induced. The typical interval from beginning of drug therapy to onset of reaction is one to three weeks.

If N-acetylation is a major metabolic pathway for lamotrigine, then slow acetylator phenotype may be a risk factor for the development of hypersensitivity reactions. Such is the case for sulfonamides which share with lamotrigine the amino group on a resonating ring. Lamotrigine is clinically even more closely related to pyrimethamine. Fansidar, a combination product



containing pyrimethamine and sulfadoxine, has been associated with severe cutaneous reactions among American travelers using it for malaria prophylaxis. Since not everyone exposed to lamotrigine or pyrimethamine develop a severe cutaneous reaction, the metabolism of these agents should be compared. Common major metabolic pathways should be explored for isozyme variants which could identify subpopulations at risk.

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Jonathan K. Wilkin, MD

cc: Jerry Collins, Ph.D.,
Director
Division of Laboratory of Clinical Pharmacology

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BEST POSSIBLE COPY



Memorandum

To: Dr. Fenney, Medical Officer
Paul Leber, MD Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research

From: Ella L. Toombs, MD, Medical Officer
Jonathan K. Wilkin, MD Director
Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research

re: Consult request dated August 26, 1997
Received from HFD 120
Delivered September 22, 1997
Reviewer receipt September 30, 1997
First Draft October 7, 1997

Dear Dr. Feeney:

In response to your question, "Please review the 18 rash cases and classify/diagnose each type...." The information received has been compiled into a table using the descriptors as provided in the case report forms. Missing data (although, not pertinent) was not obtainable.

It is the impression of this author that none of these cases can be definitively diagnosed as Stevens Johnson Syndrome based on the information given. It is possible that 3 cases may represent erythema multiforme (a less severe disease) according to the clinical description and there is one biopsy report of another case c/w same. (see table) However, I would not classify any of these cases as full blown Stephens Johnson Syndrome.

Additionally, these patients had intercurrent disease as well as concomitant medical therapy. Erythema multiforme, of which Stevens Johnson Syndrome is a variant, can be multifactorial therefore it is difficult to incriminate the study drug, exclusively.

We will be pleased to discuss this with you should you desire. Dermatology is a visually oriented speciality and it is difficult to be more precise without more complete clinical or histological data.

Thank you.

TSI
Ella L. Toombs, MD
Medical Officer-Division of Dermatologic and Dental Drug Products
Dirck, MD 10/8/97

Summary Table of Case Report Forms Submitted and Reviewed

Pt. Number	Age/sex	Days/Dose Lamictal	Cutaneous Description	Concomitant Medication	SJS (+/-)
102-51-5101	13Y/M	??	Rash	PB and CBZ	Neg
102-60-6009	11Y/M	? 90 days/50mg	Varicella Exanthem-face, torso, arms Oral mucosal bullae, conjunctivitis	CBZ, Amoxicillin/ Clavulinic acid primidone	Pos E.M
123-18-1802	11Y/F	30 days/	Rash, (stomatitis edema hands/feet, cheek bullae)	Sodium valproate Thyroxin, Amoxicillin	Pos E.M
40-02-2004	10Y/F	15 days	Rash, no blisters	Amoxicillin, Acyclovir, ibuprofen	Neg
26-9-1	8Y/F	30 days/25-150mg	Urticaria	PB, tegretol chloral hydrate	Neg
26-6-05	7Y/M		Rash	Dilantin	
26-27-03	4Y/M		Maculo-papular rash	Depakne	Neg
26-2-1	7Y/	16 days/12.5mg	Macular rash	Valproic acid	Neg
123-55-5504	7Y/M	60 days/25mg	Papulo-vesicular rash extremities, cheeks, lip - resolved 4 days	Ritalin, Depakote Tranzene	Neg
123-56-5602	10Y/F	42 days/10mg	Urethral and oral mucositis, rash, bullae Biopsy E multiforme	Valproic acid, Clonazepam	Neg Note: Biopsy
B13894	4Y/F	120 days/	Exanthem oral, genital, orbital regions, erythema antecubital and axillary regions (pain), vesicles- erosions	Sodium bromide Valproic acid, ethosuximide	Pos

40-37-01	3Y/M	56 days/280mg	Rash - mucous membranes, urticaria		Neg
40594	4Y/M	10 days/40mg	Herpangia, rash, genital blisters	Carbamazepine Sodium valproate, potassium bromide	Neg
41225	9Y/F	20 days/12-24mg	Ocular hyperemia pharyngeal erythema and pustules, rash resolved in 3 days	Promidone Valproate sodium	Neg
13043	6Y/M	14 days/5-15mg	Rash	Penicillin	Neg
4021	10/Y	?/25mg	Rash	?	Neg

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