CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020764 and 020241/S002

CHEMISTRY REVIEW(S)

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 20-764

CHEM. REVIEW # 3 | **REVIEW DATE** 11-JUN-98

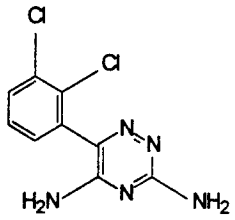
SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	17-SEP-96	19-SEP-96	
AMENDMENT	23-FEB-98	24-FEB-98	26-MAY-98
AMENDMENT	08-JUN-98	09-JUN-98	9-JUN-98

NAME AND ADDRESS OF APPLICANT
GLAXO WELLCOME Inc.
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

DRUG PRODUCT NAME
Proprietary: **LAMICTAL® CD** Chewable Dispersible Tablets
Nonproprietary/USAN: Lamotrigine
Code Name/Number: 430C78
Chem. Type/Ther. Class:

PHARMACOLOGICAL CATEGORY/INDICATION Anticonvulsant
Adjunctive treatment of secondarily generalized tonic-clonic seizures
Adjunctive treatment of Lennox-Gastaut Syndrome

DOSAGE FORM Chewable Dispersible Tablets
STRENGTHS 5, 25, and 100 mg
ROUTE OF ADMINISTRATION Oral
DISPENSED XXX RX ___ OTC



CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA
6-(2,3-Dichlorophenyl)-1,2,4-triazine -3,5-diamine

$C_9H_7Cl_2N_5$ Mol. Wt. 256.09
CAS Registry #: 84057-84-1

SUPPORTING DOCUMENTS: NDA 20-241, IND , IND
RELATED DOCUMENTS: U.S. Patent 4,602,017, expiration date 22-JUL-2003, Glaxo Wellcome Inc.

CONSULTS: The proposed trademark "LAMICTAL CD Chewable Dispersible Tablets" is acceptable by the CDER Labeling and Nomenclature Committee. The CGMP compliance status of the manufacturing facilities is ACCEPTABLE. The MV package is in preparation.

REMARKS/COMMENTS: Amendment dated 23-FEB-98 provides for responses to the Approvable letter dated 03-DEC-97. Additional information (samples of printed cartons and container labeling) is provided in the Amendment of 08-JUN-98 in response to the Agency request. Note that the info provided in these amendments applies also to NDA 20-241/S-002. The following dissolution methodology and specifications have been accepted by the sponsor: NLT ; 0.1N HCl, 900 mL, 37 ± 0.5°C; USP Apparatus II (paddle)
The expiration dating period for Lamictal Chewable Dispersible Tablets is 24 months.

CONCLUSIONS & RECOMMENDATIONS: Recommend APPROVAL of NDA 20-764. We expect sponsor's full cooperation in resolving problems that may arise during the validation of analytical methods.

APPEARS THIS WAY
ON ORIGINAL

/S/
D. Christodoulou, Ph.D., Chemist

cc: Orig. NDA 20-764
HFD-120
HFD-120/DChristodoulou
HF-120/JWare
HFD-120/MGuzewska
R/D Init by: /S/ 15.98

Filename: n20764.003

5.1

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120 SEP 15 1997
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 20-764

CHEM. REVIEW # 2 **REVIEW DATE** 30-JUL-97

SUBMISSION TYPE	**DOCUMENT DATE**	**CDER DATE**	**ASSIGNED DATE**
ORIGINAL	17-SEP-96	19-SEP-96	
AMENDMENT	01-JUL-97	03-JUL-97	07-JUL-97

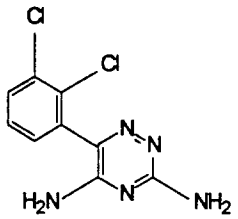
NAME AND ADDRESS OF APPLICANT GLAXO WELLCOME Research and Development

Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

DRUG PRODUCT NAME
Proprietary: **LAMICTAL® CD** Chewable Dispersible Tablets
Nonproprietary/USAN: Lamotrigine
Code Name/Number: 430C78
Chem. Type/Ther. Class:

PHARMACOLOGICAL CATEGORY/INDICATION Anticonvulsant
Adjunctive treatment of secondarily generalized tonic-clonic seizures
Adjunctive treatment of Lennox-Gastaut Syndrome

DOSAGE FORM Chewable Dispersible Tablets
STRENGTHS 5, 25, and 100 mg
ROUTE OF ADMINISTRATION Oral
DISPENSED XXX RX ___ OTC



CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA
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$C_9H_7Cl_2N_5$ Mol. Wt. 256.09
CAS Registry #: 84057-84-1

SUPPORTING DOCUMENTS: NDA 20-241, IND IND
RELATED DOCUMENTS: U.S. Patent 4,602,017, expiration date 22-JUL-2003, Glaxo Wellcome Inc.
CONSULTS: The proposed trademark "LAMICTAL CD Chewable Dispersible Tablets" is acceptable by the CDER Labeling and Nomenclature Committee. The CGMP compliance status of the manufacturing facilities is ACCEPTABLE. The MV package is in preparation.
REMARKS/COMMENTS: This amendment updates stability data (up to 12 months) for the tablets manufactured at the . The proposed protocol for the first three production batches has been modified to reduce testing. Testing at two months timepoint for samples stored at 40°C/75%RH has been deleted. The requirement for dissolution profile testing has been replaced Additionally, this amendment provides for the use of a , blister material for the commercial packaging of the tablets rather than the that was used to package tablets for stability studies.

CONCLUSIONS & RECOMMENDATIONS: Recommend APPROVAL of NDA 20-764. The 24 months' expiration dating is acceptable. We expect sponsor's full cooperation in resolving problems that may arise during the validation of analytical methods.

cc: Orig. NDA 20-764
HFD-120
HFD-120/MGuzewska
HF-120/JWare
HFD-810/CHoiberg
HFD-810/JSimmons
R/D Init by: /S 9-15-97

APPEARS THIS WAY
ON ORIGINAL

/S/

M. Guzewska, Ph.D., Chemist

Filename: n20764.002

JAN - 6 1997

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS, HFD-120
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA 20-764

CHEM. REVIEW # 1 | **REVIEW DATE** 08-OCT-96

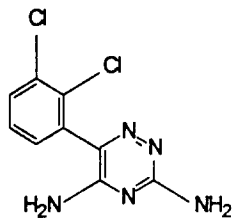
SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	17-SEP-96	19-SEP-96	23-SEP-96

NAME AND ADDRESS OF APPLICANT
GLAXO WELLCOME Research and Development
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

DRUG PRODUCT NAME
Proprietary: **LAMICTAL® CD** Chewable Dispersible Tablets
Nonproprietary/USAN: Lamotrigine
Code Name/Number: 430C78
Chem. Type/Ther. Class:

PHARMACOLOGICAL CATEGORY/INDICATION Anticonvulsant
Adjunctive treatment of secondarily generalized tonic-clonic seizures
Adjunctive treatment of Lennox-Gastaut Syndrome

DOSAGE FORM Chewable Dispersible Tablets
STRENGTHS 5, 25, and 100 mg
ROUTE OF ADMINISTRATION Oral
DISPENSED XXX RX ___ OTC



CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA
6-(2,3-Dichlorophenyl)-1,2,4-triazine -3,5-diamine

$C_9H_7Cl_2N_5$ Mol. Wt. 256.09
CAS Registry #: 84057-84-1

SUPPORTING DOCUMENTS: NDA 20-241, IND IND
RELATED DOCUMENTS: U.S. Patent 4,602,017, expiration date 22-JUL-2003, Glaxo Wellcome Inc.
CONSULTS: The assessment of a trademark was requested on 23-SEP-96 by J. Ware (CSO). The EER was sent out on 07-OCT-96 The MV package is in preparation.
REMARKS/COMMENTS: LAMICTAL® Tablets 25, 50, 100, 150, 200, and 250 mg, a compressed tablet formulation of lamotrigine, was approved on 27-DE-94 (NDA 20-241) and has been marketed in the U.S. since February 1995 for adjunctive therapy of partial seizures in adults with epilepsy. The Chewable Dispersible Tablets 5 mg, 25 mg, and 100 mg, a new dosage form for lamotrigine, are the subject of this NDA. These tablets are already marketed in Europe. LAMICTAL® Chewable Dispersible Tablets contain lamotrigine drug substance manufactured at the Glaxo facility All information concerning lamotrigine is contained in NDA 20-241 for LAMICTAL® (lamotrigine) Tablets. The chewable dispersible tablets (BP definition: "Uncoated tablets that produce a uniform dispersion in water") may be chewed, swallowed, or dispersed in a small volume of liquid for administration to patients. The 25 mg and 100 mg strength tablets The have been determined as tablets for the and , based on the sizes of clinical/biopharm/stability batches of the 5 mg tablets manufactured at these facilities. The 3-months stability data for the tablets manufactured in are insufficient to support the proposed 24 months' expiration dating (stability results for the product manufactured in are adequate).

CONCLUSIONS & RECOMMENDATIONS: Recommend NDA 20-764 APPROVABLE, subject to a satisfactory evaluation of the manufacturing facilities. The 24 months' expiration dating is justified for the drug product manufactured in Greenville, NC, but additional stability data are needed for the tablets produced in Zebulon. We expect sponsor's full cooperation in resolving problems that may arise during the validation of analytical methods.

/S/
M. Guzewska, Ph.D., Chemist

cc: Orig. NDA 20-764
HFD-120
HFD-120/MGuzewska
HF-120/JWare/CSO
HFD-120/SBlum
R/D Init by: SWB 1/13/97

APPEARS THIS WAY
ON ORIGINAL

Filename: n20764.000

MEMORANDUM of MEETING/TELEPHONE CONVERSATION

NDA #: **20-764**

PRODUCT NAME: LAMICTAL® (lamotrigine) Tablets

DATE: 07-OCT-96
CONVERSATION WITH: Beverly Lewis
FIRM NAME: Glaxo Wellcome
SUBJECT: Stability Data
PHONE #: (919) 707-7189

APPEARS THIS WAY
ON ORIGINAL

In the absence of Ms. Elizabeth McConnell, Project Director, Regulatory Affairs, I discussed the following issues with Ms. Beverly Lewis:

Sinker Device: Ms. Lewis explained that it was

Stability Batches: Ms. Lewis confirmed that the composition of all stability batches was the same as that described in the Components/Composition section of the NDA. All stability batches were manufactured according to the procedures provided in the NDA.

Stability Data: I pointed out that there was only 3 months data submitted for the tablets manufactured in . Since these tablets were placed on stability studies in December 1995, additional data should be now available. Ms. Lewis promised to check the issue and call me on Wednesday with information.

/S/

M.Guzewska, Ph.D., Chemist

APPEARS THIS WAY
ON ORIGINAL

cc: Orig. NDA 20-764
HFD-120/DivFile
JWare/CSO

File: n20764.t01

CHEMIST'S REVIEW
OF **SUPPLEMENT**

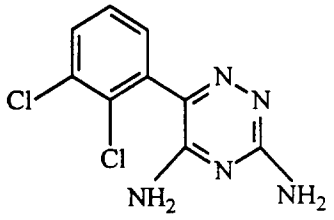
1. ORGANIZATION: HFD-120
2. NDA NUMBER: **20-241**
3. SUPPLEMENT NUMBERS/DATES: SE1-002 (AZ)
   Letterdate: 23-FEB-98
   Stampdate: 24-FEB-98
4. AMENDMENTS/REPORTS/DATES:
   Letterdate: 8-JUN-98
   Stampdate: 9-JUN-98
5. RECEIVED BY CHEMIST: 26-MAY-98

6. APPLICANT NAME AND ADDRESS: Glaxo Wellcome Inc.,
Five Moore Drive,
Research Triangle Park, NC 27709

7. NAME OF DRUG: LAMICTAL® Tablets
8. NONPROPRIETARY NAME: Lamotrigine

9. CHEMICAL NAME/STRUCTURE: 3,5-Diamino-6-(2,3-dichlorophenyl)-as-triazine

10. DOSAGE FORM(S): Tablets
11. POTENCY: 25,100, 150, 200 mg



12. PHARMACOLOGICAL CATEGORY: Antiepileptic
Adjunctive treatment of partial seizures in adults with epilepsy

13. HOW DISPENSED: XXX (XR) ___(OTC)
14. RECORDS & REPORTS CURRENT: XXX (YES) ___(NO)
15. RELATED IND/NDA/DMF: NDA 20-764

16. **SUPPLEMENT PROVIDES FOR**: responses to the Agency's Approvable Letter for SE1-002 for LAMICTAL® (Lamotrigine) Tablets.

17. COMMENTS: The SE1-002 incorporates by reference the clinical data contained in NDA 20-764, (LAMICTAL® Chewable Dispersible Tablets) so that the approved tablets can be used for a new indication (adjunctive treatment of Lennox-Gastaut syndrome in pediatric and adult patients). This cross-reference allows for the development of one label for both lamotrigine products (NDA 20-764 and NDA 20-241).

18. CONCLUSIONS AND RECOMMENDATIONS: Recommend **APPROVAL** of NDA 20-241/S-002

19. REVIEWER NAME | SIGNATURE | DATE COMPLETED

Danae D. Christodoulou /S/ 11-JUNE-98

cc: Orig. NDA 20-241
HFD-120/DivFile
HFD-120/J Ware
HFD-120/DChristodoulou
INIT: MG 6.11.98

APPEARS THIS WAY
ON ORIGINAL

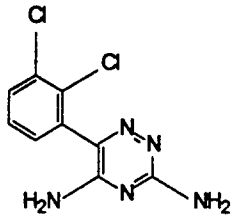
filename:n20241s.002

CHEMIST REVIEW
OF **SUPPLEMENT**

1. ORGANIZATION: HFD-120
2. NDA NUMBER: **20-241**
4. SUPPLEMENT NUMBERS/DATES: SEI-002
   Letterdate: 16-SEP-96
   Stampdate: 17-SEP-96
5. AMENDMENTS/REPORTS/DATES:
6. RECEIVED BY CHEMIST: 23-SEP-96

7. APPLICANT NAME AND ADDRESS: GLAXO WELLCOME Research and Development
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

8. NAME OF DRUG: **LAMICTAL® Tablets**



9. NONPROPRIETARY NAME: lamotrigine

10. CHEMICAL NAME/STRUCTURE: 6-(2,3-Dichlorophenyl)-1,2,4-triazine -3,5-diamine

11. DOSAGE FORM(S): Tablets

12. POTENCY: 25, 50, 100, 150, 200 and 250 mg

13. PHARMACOLOGICAL CATEGORY: Anticonvulsant
Adjunctive treatment of secondarily generalized tonic-clonic seizures
Adjunctive treatment of Lennox-Gastaut Syndrome

14. HOW DISPENSED: XXX (RX) ____ (OTC)

15. RECORDS & REPORTS CURRENT: XXX (YES) ____ (NO)

16. RELATED IND/NDA/DMF: IND , IND NDA 20-764 (Lamictal CD Chewable Dispersible Tablets)

17. **SUPPLEMENT PROVIDES FOR**: Environmental Assessment for LAMICTAL® (lamotrigine) Tablets to be used in the treatment of Lennox-Gastaut Syndrome and Secondary Generalized Seizures.

18. COMMENTS: LAMICTAL® Tablets, a compressed tablet formulation of lamotrigine, have been marketed in the United States since 1995 for adjunctive therapy of partial seizures in adults with epilepsy. This supplemental EA discusses only the impact of the new indication on the environmental assessment submitted with the original NDA 20-241. Environmental Assessment and FONSI are attached. The provided EA information is acceptable.

19. CONCLUSIONS AND RECOMMENDATIONS: Recommend APPROVAL of NDA 20-241/S-002

20. REVIEWER NAME: Maria E. Guzewska
SIGNATURE: /S/
DATE COMPLETED: 07-OCT-96

APPEARS THIS WAY
ON ORIGINAL

cc: Original: NDA 20-241
HFD-120/DivFile
HFD-120/JWare
HFD-120/MGuzewska
INIT: SWB /S/ 10/11/96

filename: n20241.002

OUTGOING

SEP 24 1996

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 23, 1996

FROM: Paul Leber, M.D., Director, /S/ 9/23/96
Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

TO: Dan Boring, Chair
Labeling and Nomenclature Committee
HFD-530, Corporate 2, Rm N461
301-827-2391

APPEARS THIS WAY
ON ORIGINAL

Proposed Trademark: **Lamictal® CD Chewable Dispersible Tablets**
Established name, including dosage form: **lamotrigine chewable dispersible tablets**
Other trademarks by the same firm for companion products: **Lamictal® tablets**
Indications for Use (may be a summary if proposed statement is lengthy):

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.

Initial comments from the submitter: (concerns, observations, etc.) **"Glaxo Wellcome requests Agency comments on the acceptability of the proposed proprietary name for lamotrigine chewable/dispersible tablets, LAMICTAL® CD (lamotrigine) Chewable Dispersible Tablets."**

cc:
ORIG NDA
HFD-120
HFD-120/SBlum/MGuzewska
HFD-120/JWare
file: a:\N20-764\20764nam.c1

APPEARS THIS WAY
ON ORIGINAL

/S/ 9/24/96

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.

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

APPEARS THIS WAY
ON ORIGINAL