CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020241/S003 AND 020764/S001

CHEMISTRY REVIEW(S)

CHEMIST REVIEW
OF **SUPPLEMENT**

1. ORGANIZATION: HFD-120
2. NDA NUMBER: **20-241**
4. SUPPLEMENT NUMBERS/DATES: SEI-003
   Letterdate: 24-FEB-97
   Stampdate: 25-FEB-97
5. AMENDMENTS/REPORTS/DATES:
6. RECEIVED BY CHEMIST: 04-MAR-97

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

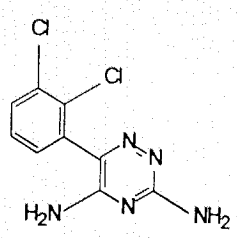
8. NAME OF DRUG: **LAMICTAL® Tablets**

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
Monotherapy of partial seizures in adults with epilepsy

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 as monotherapy of partial seizures in adult patients (≥13 years old).

18. COMMENTS: LAMICTAL® Tablets, a _____ tablet formulation of lamotrigine, have been marketed in the United States since 1995 for adjunctive therapy of partial seizures in adults with epilepsy. The currently approved CM&C for LAMICTAL® Tablets are unchanged by this supplemental application, except for an updated EA to address a possible increase in use of the drug as monotherapy for treatment of partial seizures in adults with epilepsy. The provided EA information is acceptable.

19. CONCLUSIONS AND RECOMMENDATIONS: Recommend APPROVAL of NDA 20-241/S-003

20. REVIEWER NAME: Maria E. Guzewska

SIGNATURE: /S/

DATE COMPLETED: 10-MAR-97

cc: Original: NDA 20-241
HFD-120/DivFile
HFD-120/JWare
HFD-120/MGuzewska
INIT: SWP /S/ 3/14/97

APPEARS THIS WAY
ON ORIGINAL

filename: n20241.003

ENVIRONMENTAL ASSESSMENT

NDA 20-241/S-003

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

1. **DATE**: Original: 22-JAN-93
Supplemental: 31-JAN-97

2. **NAME of APPLICANT**:: Glaxo Wellcome, Inc.

3. **ADDRESS**: Five Moore Drive, Research Triangle Park, NC 27709

4. **DESCRIPTION of the PROPOSED ACTION**

4a/b. Description of Requested Approval and Need for Action: Supplement SEI-003 provides for the use of LAMICTAL® (lamotrigine) Tablets 25, 50, 100, 150, 200, and 250 mg as monotherapy of partial seizures in adult patients. This product is currently marketed 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 NDA 20-241.

4c. Location where Products will be Produced: Information in this section remains unchanged from the information provided in Section 4.c. of the original EA for LAMICTAL® (lamotrigine) Tablets.

4d. Sites of Products Use: Information in this section remains unchanged from the information provided in Section 4.d. of the original EA for LAMICTAL® (lamotrigine) Tablets.

4e. Sites of Disposal: Returned and expired drug product is destroyed at the Glaxo Wellcome facility in Greenville, North Carolina by a controlled air incinerator. The incinerator operates under permit number 74-03-I issued by the NC Division of Solid Waste. The permit expires July 7, 1997.

5. IDENTIFICATION of CHEMICAL SUBSTANCES that are the SUBJECT of the PROPOSED ACTION: Information in this section remains unchanged from the information provided in Section 5 of the original EA for LAMICTAL® (lamotrigine) Tablets.

6. INTRODUCTION of SUBSTANCES into the ENVIRONMENT

6a. Substances Expected to be Emitted: Information in this section remains unchanged from the information provided in Section 6a(1) of the original EA for LAMICTAL® (lamotrigine) Tablets.

6b. Controls Exercised: Information in this section remains unchanged from the information provided in Section 6a(2) of the original EA for LAMICTAL® (lamotrigine) Tablets.

6c. Citation and Statement of Compliance with Emission Requirements: Information in this section remains unchanged from the information provided in Section 6a(3) of the original EA for LAMICTAL® (lamotrigine) Tablets.

6d. Effect of Approval on Compliance with Emission Requirements: Information in this section remains unchanged from the information provided in Section 6a(4) of the original EA for LAMICTAL® (lamotrigine) Tablets. Although more drug may be needed to support the requested approval, emission requirements will remain unchanged because they are based on emission concentrations and per batch emission concentrations will remain unchanged.

6e. Expected Introduction Concentrations: The expected introduction concentration (EIC) for the aquatic compartment of lamotrigine from all LAMICTAL® products in the fifth year production is:

EIC - Aquatic (ppm) =

The value was calculated using the following equation:

EIC - Aquatic (ppm) = (A)(B)(C)(D)

where: A = kg/yr production
B = 1/liters/day entering POTW's =
C = year/365 days
D = 10^6 mg/kg (conversion factor)

It is estimated that there will be no emission to the environment from product disposal. All product in the United States that is returned or rejected is completely destroyed by high-temperature incineration at the facilities and under the permits discussed in Section 4e.

7 - 11. Information is not required because the EIC from use and disposal are expected to be less than 1 ppb.

12. LIST of PREPARERS: Horace G. Rozier Jr., Environmental Engineer, Glaxo Wellcome, Inc.

13. CERTIFICATION: Signed on January 30, 1997 by: Thomas F. Cecich, Vice President, Environmental Safety, Glaxo Wellcome Inc.

14. REFERENCES: Provided

APPEARS THIS WAY
ON ORIGINAL

CONCLUSIONS and RECOMMENDATIONS: The information provided is complete and acceptable. Recommend approval of Environmental Assessment for NDA 20-241/S-003 [LAMICTAL® (lamotrigine) Tablets].

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020241/S003 AND 020764/S001

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

and

FINDING OF NO SIGNIFICANT IMPACT

for

LAMICTAL® (lamotrigine) Tablets

25, 50, 100, 150, 200, and 250 mg

NDA 20-241/S-003

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION HFD-120

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-241/S-003

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

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their supplemental new drug application for LAMICTAL® (lamotrigine) Tablets, Glaxo Wellcome Inc. has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31 a (a) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Lamotrigine is a drug indicated in the adjunctive treatment of partial seizures in adults with epilepsy. The requested approval of the Supplemental NDA will allow the product to be marketed for Monotherapy of partial seizures in adults with epilepsy.

The drug substance is manufactured at . The drug product is formulated and packaged at the Burroughs Wellcome Co.'s Greenville, North Carolina, facility. The finished drug product is intended primarily for home care use throughout the United States. Occasional use will occur in hospitals.

Lamotrigine will enter the environment as the result of manufacture and use. Information regarding disposal of production waste and returned goods is included in environmental assessment. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic procedures. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which includes landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

Precautions taken at the sites of manufacture of the bulk drug and its final formulation are expected to minimize occupational exposures and environmental release.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

DETIDN

MAY 20 1997 4

3.10.97
DATE

/S/

Maryla Guzewska, Ph.D.
Chemist, HFD-120

3/10/97
DATE

/S/

DIVISION CONCURRENCE
Stanley W. Blum, Ph.D.
Team Leader, HFD-810/HFD-120

3/18/97
DATE

/S/

APPROVED
Nancy B. Sager
Acting Supervisor
Environmental Assessment Team
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Attachments: Environmental Assessment
FOI - Releasable EA

APPEARS THIS WAY
ON ORIGINAL

cc: HFD-120/Original NDA 20-241
HFD-120/Division File
HFD-120/MGuzewska
HFD-120/JWare
HFD-120/SBlum
HFD-357/FONSI File (NDA 20-241)
HFD-357/Docket File
HFD-205/FOI Copy

SUPPLEMENTAL ENVIRONMENTAL ASSESSMENT

LAMICTAL ® (lamotrigine) Tablets

NDA 20-241

TABLE OF CONTENTS

1. DATE

January 31, 1997

2. APPLICANT

Glaxo Wellcome Inc.

3. ADDRESS

Five Moore Drive
Research Triangle Park, NC 27709

4. DESCRIPTION OF THE PROPOSED ACTION

4.a. Description of Requested Approval

Glaxo Wellcome Inc. has filed an supplemental NDA pursuant to Section 505(b) of the Food, Drug and Cosmetic Act for LAMICTAL® (lamotrigine) Tablets to be marketed for Monotherpy of partial seizures in adults with epilepsy at the current approved strengths of 25, 50, 100, 150, 200, and 250 mg. On November 3, 1993, the final environmental assessment for NDA 20-241 LAMICTAL® (lamotrigine) Tablets was submitted to the FDA pursuant to 21 CFR Part 25.31 a(a). As provided for in the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995), this supplemental EA discusses only the impact of the new indication on the environmental assessment submitted with NDA 20-241.

A supplemental EA was submitted on August 8, 1994 and has since been approved for the marketing of LAMICTAL® Tablets in the 25 and 50mg tablet strengths. A separate supplement was submitted on September 16, 1996 to market LAMICTAL® Tablets as an aid for Lennox Gastaut Syndrome and secondary generalized seizures. This supplement is still awaiting approval. These supplements are included as Attachments 2 and 3 respectively.

4.b. Need for the Action

LAMICTAL® (lamotrigine) Tablets is indicated in the adjunctive treatment of partial seizures in adults with epilepsy. The requested approval will allow the product to be marketed for Monotherapy of partial seizures in adults with epilepsy.

4.c. Locations where Products will be Produced

Information in this section remains unchanged from the information provided in Section 4.c of the original EA for LAMICTAL® (lamotrigine) Tablets (Attachment 1).

4.d. Sites of Product Use

Information in this section remains unchanged from the information provided in Section 4.d of the original EA for LAMICTAL® (lamotrigine) Tablets (Attachment 1).

4.e. Sites of Disposal

Returned and expired drug product is destroyed at the Glaxo Wellcome facility in Greenville, North Carolina. The facility is located northeast of the city of Greenville in Pitt County, North Carolina at the intersection of U.S. 13 North and State Road 1590. Pitt County is located in eastern North Carolina. The city of Greenville, with an estimated 1990 population of 48,000, is located in the center of the county approximately 50 kilometers southeast of Rocky Mount. Since the plant site is located in the coastal plain region of the state, terrain is extremely flat with terrain elevations changing only a few feet within a few kilometers of the plant site. The facility is located in an area zoned industrial. To the west-northwest of the facility the land is zoned Residential/Agricultural. The returned drug is destroyed by a controlled air incinerator which operates at temperatures ranging from 1200°F in the primary chamber to 1850°F in the secondary chamber. The incinerator operates under permit number 74-03-I issued by the N.C. Division of Solid Waste. The permit expires July 7, 1997. The address of the facility is:

Glaxo Wellcome Inc.
Corner of U.S. 13/NC11 and State Road 1590
Greenville, North Carolina 27834

5. IDENTIFICATION OF CHEMICAL SUBSTANCES

Information in this section remains unchanged from the information provided in Section 5. of the original EA for LAMICTAL® (lamotrigine) Tablets (Attachment 1).

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

6.a. Substances Expected To Be Emitted

Information in this section remains unchanged from the information provided in Section 6.a(1) of the original EA for LAMICTAL® (lamotrigine) Tablets (Attachment 1).

6.b. Controls Exercised

Information in this section remains unchanged from the information provided in Section 6.a(2) of the original EA for LAMICTAL® (lamotrigine) Tablets (Attachment 1).

6.c. Citation And Statement Of Compliance With Applicable Emission Requirements

Information in this section remains unchanged from the information provided in Section 6.a(3) of the original EA for LAMICTAL® (lamotrigine) Tablets (Attachment 1).

6.d. Effect Of Approval On Compliance With Current Emission Requirements

Information in this section remains unchanged from the information provided in Section 6.a(3) of the original EA for LAMICTAL® (lamotrigine) Tablets (Attachment 1). Although more drug product may be needed to support the requested approval emission requirements are based on emission concentrations. Per batch emission concentrations will remain unchanged.

6.e. Expected Introduction Concentrations

6.e.i. Expected Introduction Concentrations From Use

Calculations of the Expected Introduction Concentration (EIC) for the aquatic compartment are included as CONFIDENTIAL information in Attachment A. Attachment A shows that the EIC, calculated using the forecasts for all lamotrigine products and indications including Monotherapy is

6.e.ii. Introductions from Product Disposal

It is estimated that there will be no emission to the environment from product disposal. All product in the United States that is returned or rejected is completely destroyed by high-temperature incineration at the facilities and under the permits discussed in Section 4.e .

7. FATE OF SUBSTANCES IN THE ENVIRONMENT

As provided for in Section III.D.7.c of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995) EA Sections 7, 8, 9, 10, 11 and 15 are not required because the EIC from use and disposal are expected to be

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

As provided for in Section III.D.7.c of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995) EA Sections 7, 8, 9, 10, 11 and 15 are not required because the EIC from use and disposal are expected to be

9. USE OF RESOURCES AND ENERGY

As provided for in Section III.D.7.c of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995) EA Sections 7, 8, 9, 10, 11 and 15 are not required because the EIC from use and disposal are expected to be

10. MITIGATION MEASURES

As provided for in Section III.D.7.c of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995) EA Sections 7, 8, 9, 10, 11 and 15 are not required because the EIC from use and disposal are expected to be

11. ALTERNATIVES TO THE PROPOSED ACTION

As provided for in Section III.D.7.c of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995) EA Sections 7, 8, 9, 10, 11 and 15 are not required because the EIC from use and disposal are expected to be

12. LIST OF PREPARERS

This EA was prepared by:

APPEARS THIS WAY
ON ORIGINAL

HORACE G. ROZIER Jr.

- Certified Hazardous Material Manager
- Environmental Engineer, Glaxo Wellcome Inc. 1993 - present
- Chemist, Ecoflo Inc. 1989-1993
- Chemist, Compuchem Environmental Corporation 1989
- Bachelor of Science in Biochemistry & Microbiology
  North Carolina State University , 1989

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

13. CERTIFICATION

The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of Glaxo Wellcome Inc.

The undersigned official certifies that the EA summary document pages 1-5 and Attachments 1-3 contain non-confidential information and acknowledges that this information will be made available to the public in accordance with 40 CFR 1506.6.

Thomas F. Cecich

1/30/97

Date

Vice President, Environmental Safety
Glaxo Wellcome Inc.

14. REFERENCES

Center for Drug Evaluation and Research, "Guidance For Industry For the Submission Of An Environmental Assessment In Human Drug Applications And Supplements," Federal Register, November 1995

Council On Environmental Quality, " Regulations On Implementing National Environmental Policy Act Procedures," Federal Register, Vol. 43, November 29, 1978, p. 55990.

Pharmaceutical Manufacturers Association, "Interim Guidance To The Pharmaceutical Industry For Environmental Assessment Compliance Requirements For The FDA v7," Seminar on Environmental Assessments, Rockville, Md., July 29-30, 1991.

U.S. FDA, "Environmental Assessment Technical Assistance Handbook, U.S. FDA, March 1987

U.S. FDA, "National Environmental Policy Act; Policies and Procedures; Final Rule," Federal Register, Vol. 50, April 26, 1985

15. APPENDIXES

As provided for in Section III.D.7.c of the Guidance For Industry For The Submission Of An Environmental Assessment In Human Drug Applications And Supplements (FDA, 1995) EA Sections 7, 8, 9, 10, 11 and 15 are not required because the EIC from use and disposal are expected to be

55 Pages Removed

Attachment I & II Available in SBA of N20241

Attachment III available in approval package of N20241 5002