CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-711

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

JAN 25

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

QUITAB (Bupropion SR Tablets), 50,100 and 150 mg

NDA 20-711

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION HFD-170

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-711

QUITAB (Bupropion SR Tablets), 50, 100 and 150 mg

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decisionmaker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

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.

Glaxo Wellcome Inc., has prepared environmental assessment in support of their new drug application for QUITAB (Bupropion SR Tablets), 50, 100 and 150 mg intended as twice a day administration for nicotine smoking cessation indication. The EA has evaluated the potential environmental impacts of the manufacture, use and disposal of the drug product.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

12.17.96
DATE

P. Maturu
PREPARED BY
[P.Maturu, PhD]
[Review Chemist]
[HFD-170 DIVISION]

1/9/97
DATE

CONCURRENCE
[A. D'Sa, PhD]
[Chemistry Team Leader]
[HFD-170 DIVISION]

1/25/97
DATE

Nancy B Sager
CONCURRENCE
Nancy B. Sager
Environmental Scientist
Center for Drug Evaluation and Research

Attachment: Environmental Assessment
Material Safety Data Sheet (drug substance)
EA/FONSI for NDA 20-358

CC: FONSI for NDA 20-711

Original NDA 20-711/HFD-170 through BMcNeal
HFD-170/Division File(s)
HFD-170/PMaturu, AD'Sa, BMcNeal
FONSI File NDA 20-711/HFD-357
Docket File 20-711/HFD-357
FOI Copy HFD-205

ENVIRONMENTAL ASSESSMENT

TRADENAME (bupropion hydrochloride) Sustained-Release Tablets

TABLE OF CONTENTS

1. DATE

March 15, 1996

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 NDA pursuant to Section 505(b) of the Food, Drug and Cosmetic Act for TRADENAME (bupropion hydrochloride) Sustained-Release Tablets, 50 mg, 100 mg, and 150 mg to be marketed as an aid to smoking cessation. Bupropion hydrochloride is currently indicated for the treatment of depression. It has been marketed as an Immediate-Release Tablet since 1989. On September 22, 1995, the original environmental assessment (EA dated July 27, 1995) for NDA 20-358 (WELLBUTRIN Sustained-Release Tablets) was submitted to the FDA. This submission was made 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 EA discusses only the impact of the new indication on the environmental assessment submitted with NDA 20-358.

4.b. Need for the Action

Bupropion hydrochloride is indicated for the treatment of depression. The requested approval will allow the product to be marketed as an aid to smoking cessation.

4.c. Locations where Products will be Produced

Information in this section remains unchanged from the information provided in Section 4.c(1) and 4d of the original EA for WELLBUTRIN Sustained-Release Tablets (Attachment 1).

4.d. Sites of Product Use

Information in this section remains unchanged from the information provided in Section 4.c(2) of the original EA for WELLBUTRIN Sustained-Release Tablets (Attachment 1).

4.e. Sites of Disposal

Disposal of returned or rejected drug product will be accomplished through on-site incineration. Disposal of returned or rejected product through the waste treatment system will not occur. Information on sites of incineration remains unchanged from the information provided in Section 4.c(3) of the original EA for WELLBUTRIN Sustained-Release Tablets (Attachment 1).

5. IDENTIFICATION OF CHEMICAL SUBSTANCES

Information in this section remains unchanged from the information provided in Section 5 of the original EA for WELLBUTRIN Sustained-Release 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 WELLBUTRIN Sustained-Release 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 WELLBUTRIN Sustained-Release 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 WELLBUTRIN Sustained-Release 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.b of the original EA for WELLBUTRIN Sustained-Release Tablets (Attachment 1). Although more drug product will 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 combined forecasts for WELLBUTRIN Immediate-Release, WELLBUTRIN Sustained-Release Tablets and TRADENAME Sustained-Release Tablets for both depression and smoking cessation, is less than 1 ppb.

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

The major route of drug substance emission into the environment is via excretion in the urine and feces following product use and subsequent release into wastewater collection and treatment systems. Because the water solubility of the drug substance is greater than 10^{-5} molar and the octanol/water partition coefficient is less than 2 (see Section 7. of Attachment 1) any drug substance not treated in the wastewater treatment plant should enter the aquatic environment. As discussed in Section 6.e.i the EIC for the aquatic compartment is expected to be less than 1 ppb. The maximum expected environmental concentration (EEC) will be less than the EIC since the photodegradation half life is less than 3 days (see Section 7.a of Attachment 1).

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 less than 1ppb.

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 less than 1ppb.

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 less than 1ppb.

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 less than 1ppb.

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 less than 1ppb.

12. LIST OF PREPARERS

This EA was prepared by:

DOUGLAS S. FINAN

- Manager, Environmental Affairs, Glaxo Wellcome Inc.
  1991 - present
- Environmental Safety Engineer, Glaxo Wellcome Inc.
  1990 - 1991
- Environmental Engineer, North Carolina Division of Environmental Management
  1979-1990
- Environmental Specialist, Deltona Corporation
  1978-79
- Bachelor of Science in Environmental Science & Engineering
  Florida Institute of Technology, 1978

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 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 — March 20, 1996

Thomas F. Cecich — Date

Vice President, Environmental Safety
Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

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 Vol. 7," 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 less than 1ppb.

ATTACHMENT

Referenced FONSI/EA for NDA 20-358

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

WELLBUTRIN™

(bupropion hydrochloride)

Sustained Release Tablets

50, 100 and 150 mg

NDA 20-358

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF NEUROPHARMACOLOGICAL
DRUG PRODUCTS (HFD-120)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-358

WELLBUTRIN

(bupropion hydrochloride)

Sustained Release Tablets

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 new drug application for **WELLBUTRIN Sustained Release Tablets**, **Burroughs Wellcome Co.** has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Bupropion hydrochloride is a synthetic drug which is administered orally in the treatment of depression. The drug substance and drug product will be manufactured and packaged by Burroughs Wellcome Co., Greenville, NC. The finished drug product will be used in hospitals, clinics and homes.

Bupropion hydrochloride may enter the environment from excretion by patients, as emissions from manufacturing sites or from disposal of pharmaceutical wastes. Chemical and physical test results indicate that the majority of the drug substance will be restricted to the aquatic environment. Data indicate that the material has the potential to rapidly photodegrade and will not persist in the environment.

The toxicity of the material to microorganisms was characterized and no inhibitory effects are anticipated at the expected environmental concentrations.

Disposal may result from production waste such as out of specification lots, returned or expired product, and user disposal of empty or partly used product and packaging. Pharmaceutical waste and returned or expired product will be disposed of by the manufacturer at a licensed incineration facility or expired or rejected drug product may be destroyed by shredding and rinsing followed by wastewater treatment. At U.S. hospitals or clinics empty or partially empty packages will be disposed according to hospital procedures. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include 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 product 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.

10/26/95 _____
DATE PREPARED BY
Nancy B. Sager
Environmental Scientist
Center for Drug Evaluation and Research

10/26/95 _____
DATE CONCURRED
Roger L. Williams, M.D.
Center for Drug Evaluation and Research

Attachment: Environmental Assessment

c.c. original NDA 20-358/PDavid copy to NDA/HFD-120
HFD-004/FONSI File NDA #20-358
HFD-004/Docket File
HFD-019/FOI COPY

NDA 20-711

No Federal Register Notices or OTC documents were prepared for this product.

NDA 20-711

No advertising materials were submitted to the agency for this NDA prior to approval.