

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020500/S005

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

ITEM 18
User Fee Cover Sheet

**Statutory Exemption from User Fees
for Supplemental New Drug Application
for MEPRON (atovaquone)
for the Prevention of *Pneumocystis carinii* pneumonia (PCP)**

Pursuant to the Prescription Drug User Fee Act, as amended by Section 103(a)(2)(C) of the Food and Drug Administration Modernization Act of 1997, this Supplemental New Drug Application is statutorily exempt from user fees because the drug substance (atovaquone, MEPRON, 566C80) and indication (prevention of *Pneumocystis carinii* pneumonia (PCP)) has previously been granted an Orphan Drug designation by the Office of Orphan Products Development.

GlaxoWellcome

DESK COPY

November 12, 1998

Mark Goldberger, M.D., Director
Division of Special Pathogens & Immunologic Drug Products
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
HFD-590
9201 Corporate Blvd.
Rockville, MD 20850

**Re: NDA 20-500/S-005; MEPRON® (atovaquone) Suspension
Response to FDA Request/Comment: Clinical, Statistical
Patients on Dapsone in Study GW115-211**

Dear Dr. Goldberger:

Reference is made to the facsimile received from FDA on November 5, 1998, and to a teleconference held between Dr. Roopa Viraraghavan (Medical Reviewer) and Ms. Atkins of your Division and Dr. Jeff Chulay (Project Leader), Ms. Janna Scott (Project Statistician) and myself of Glaxo Wellcome to discuss a statistical request for Study GW115-211. Dr. Viraraghavan requested separate analysis for the two possible treatments for the dapsone arm in Study GW115-211: dapsone alone and dapsone plus pyrimethamine and folinic acid. Specifically, she asked for the ITT and as treated primary analyses for the two groups listed above, looking at PCP and safety endpoints, to be sure that the label accurately describes the treatment comparisons based on the actual drugs used and endpoints obtained by the various treatment regimens. The request included the frequency of treatment limiting adverse events and the number of patients who discontinued therapy.

We are submitting herewith the requested statistical analysis, in Attachment 1. In addition, a list of all patients in Study GW115-211 who were either positive for toxoplasmosis at baseline or who had a CD4+ cell count <100 cells at baseline is included in Attachment 2. A diskette containing electronic files of these tables is also included.

In our analysis of this data, there are no differences between these dapsone subgroups, nor do they differ from the analyses submitted in the NDA. The total columns of these tables match with the dapsone column of the original submission.

Glaxo Wellcome Research and Development

Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

Telephone
919 483 2100

A Division of
Glaxo Wellcome Inc.

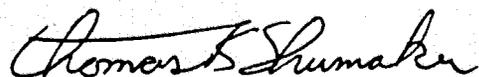
Mark Goldberger, M.D.

November 12, 1998

Page 2

This submission is provided in hard copy in duplicate, including one copy with a diskette for the NDA file. Four desk copies, including one copy of the diskette, have been sent directly to Ms. Brenda Atkins for use by the review team. If you have any questions regarding this submission, please telephone me at (919) 483-9324. Thank you.

Sincerely,

A handwritten signature in cursive script that reads "Thomas K. Shumaker".

Thomas K. Shumaker

Project Director

Regulatory Affairs

GlaxoWellcome

March 5, 1998

Mark Goldberger, M.D., Acting Director
Division of Special Pathogens and Immunologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room, HFD-590
9201 Corporate Boulevard, Fourth Floor
Rockville, MD 20850

**Re: NDA 20-500; MEPRON® (atovaquone) Suspension
Supplemental New Drug Application for the
Prevention of *Pneumocystis carinii* Pneumonia (PCP)**

Dear Dr. Goldberger:

We are herewith submitting a supplemental new drug application for the use of MEPRON Suspension for the prevention of *Pneumocystis carinii* pneumonia (PCP). MEPRON Suspension was previously approved for the treatment of PCP on 8 February 1995. The content and format of this Supplemental Application have been prepared in accordance with the provisions of 21 CFR 314.50, and are based on a proposal sent to the Division on 5 August 1997 and discussed and amended at a pre-NDA meeting held 24 September 1997 and in subsequent telephone conversations with the Division.

The purpose of this Supplemental Application is to seek approval for the use of MEPRON Suspension for the prevention of PCP in accordance with 21 CFR 314.70(b). We are submitting the results of two adequate and well-controlled trials (GW115-211 and GW115-213) that verify and describe the clinical benefits of MEPRON Suspension for this indication.

By agreement with the Division, a CMC Supplemental Application, for a 10mL unit dose pack sachet, to support the dosage regimen proposed in this clinical supplement was previously submitted for review on 19 January 1998. The current submission contains labeling and printed artwork/labels for the 10mL sachet, which were not included in the 19 January 1998 submission. Our current understanding of the agreement is that the 10mL sachet portion of the 19 January 1998 submission will receive action coincident with the action on this clinical supplement.

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Mark Goldberger, M.D.

March 5, 1998

Page 2

In accordance with the provisions of the Prescription Drug User Fee Act, as amended by Section 103(a)(2)(C) of the Food and Drug Administration Modernization Act of 1997, this Supplemental New Drug Application is statutorily exempt from user fees because the drug and indication was previously granted Orphan Drug designation by the Office of Orphan Drug Development. Therefore, no user fee has been paid for review of this Supplement to NDA 20-500. Documentation of this fact is included in Volume 1 of this Supplement.

This submission is provided in duplicate, with the exception that Item 12 is provided as a single electronic archival copy. Review copies of Volume 1 plus Item 8 or 10 are also provided for the Medical Officer and Statistician, respectively. Four desk copies of Volume 1 have been provided directly to Ms. Atkins. In addition, electronic review copies on the proposed package insert, the Item 3 Summary, the Integrated Summary of Efficacy, the Integrated Summary of Safety, and Other Studies and Information section of Item 8 and the text and tables of the two pivotal studies are being provided directly to Ms. Atkins for reviewer convenience, as agreed at the 24 September 1997 pre-NDA meeting. Please contact me at 919-483-9324 for any matters regarding this application.

We appreciate the Division's guidance to date in supporting our efforts to prepare and submit this application. We have used your guidance in the interest of preparing a complete and reviewer-friendly application that will facilitate your review. We look forward to working with you during the review process.

Sincerely,



Thomas K. Shumaker
Project Director
Regulatory Affairs

GlaxoWellcome

DESK COPY

December 15, 1998

Mark Goldberger, M.D., Director
Division of Special Pathogens & Immunologic Drug Products
Center for Drug Evaluation and Research
Attn: Document Control Room
Food and Drug Administration
HFD-590
9201 Corporate Blvd.
Rockville, MD 20850

**Re: NDA 20-500/S-005; MEPRON® (atovaquone) Suspension
Response to FDA Request/Comment: Revised Labeling**

Dear Dr. Goldberger:

Reference is made to the facsimile received from your Division on December 7, 1998, consisting of FDA labeling revisions to the July 28, 1998 annotated version of the package insert for the above referenced product. Reference is also made to the Glaxo Wellcome response to this labeling, submitted December 11, 1998 and to the teleconference held on December 14, 1998 between members of your Division and staff of Glaxo Wellcome Inc. to discuss and agree the final wording for this package insert.

We have incorporated all of the Division's suggested changes, which were also agreed to by Glaxo Wellcome prior to the December 14 teleconference, into a clean base copy, which is included in Attachment 1 to this submission. Revision bars and underlining are used to indicate those sections of the label where agreement was reached during the teleconference. With the Agency's concurrence, Glaxo Wellcome considers this labeling to be final. A clean copy of the label is included in Attachment 2.

We would like to thank the Division for affording us the opportunity to discuss their current thinking regarding pediatric labeling for MEPRON Suspension during the labeling teleconference. This information will be useful to the Company in future efforts to support adequate labeling for this product in this underserved population.

Also included in this submission, in Attachment 3, is the color printed artwork for the package cartons for the 10mL unit dose sachet. Color printed artwork for the sachet foils was previously submitted for review by Dr. Norman Schmuff on August 14, 1998. This presentation was included, and approved, concurrent with the 5mL unit dose sachet in Supplement S-004 (submitted January 19, 1998; approved September 14, 1998). This

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Mark Goldberger, M.D.

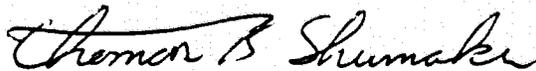
December 15, 1998

Page 2

presentation has not been introduced into trade, pending approval of the current Supplement, S-005, for the prophylaxis of *Pneumocystis carinii* pneumonia indication.

This submission is provided in duplicate, with one archival copy of the labeling diskette. Four additional desk copies and a labeling diskette have been sent directly to Ms. Brenda Atkins for use by the review team. If you have any questions regarding this submission, please contact me by telephone at (919) 483-9324.

Sincerely,



Thomas K. Shumaker
Project Director
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

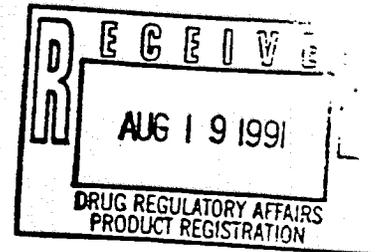
DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of Orphan Products Development (HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

August 14, 1991

Burroughs Wellcome Company
Attention: Mr. Randy Vestal
Drug Regulatory Affairs
3030 Cornwallis Road
Research Triangle Park, NC 27709



Dear Mr. Vestal:

Reference is made to your orphan drug application of July 3, 1991, submitted pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb) for the designation of 566C80 as an orphan drug amendment dated April 11, 1991. We also refer to your

We have completed the review of this amendment and have determined that 566C80 qualifies for orphan designation for the prevention of *Pneumocystis carinii* pneumonia (PCP) in high-risk, HIV-infected patients defined by one or both of the following criteria: (1) a history of one or more episodes of PCP, (2) a peripheral CD4+ (T4 helper/inducer) lymphocyte count less than or equal to 200/mm³. Please refer to this letter as official notification of designation.

Prior to marketing approval, sponsors of designated orphan products are requested to submit written notification to this Office of their intention to exercise orphan drug exclusivity if they are the first sponsor to obtain such approval for the drug. This notification will assist FDA in assuring that approval for the marketing of the same drug is not granted to another firm for the statutory period of exclusivity. Also please be advised that if 566C80 were approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA (21 U.S.C. 360cc). Therefore, in order to avoid discrepancies between the designated orphan indication and the proposed marketing indication, sponsors of designated orphan products have the option to submit data to amend their orphan designation prior to marketing approval.

In addition, please inform this office annually as to the status of the development program, and at such time as a marketing application is submitted to the FDA for the use of 566C80 as designated. If you need further assistance in the development of your product for marketing, please feel free to contact Dr. Donald R. Haggerty at (301) 443-1718.

Congratulations on obtaining your orphan drug designation.

Sincerely yours,

/S/

Marlene E. Häffner, M.D., M.P.H.
Director

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ITEM 13

**Patent Information on Any Patent Which Claims the Drug
[21 U.S.C. 355 (b) or (c)]**

**Patent Information on Product
of
Glaxo Wellcome Inc.
5 Moore Drive
Research Triangle Park, NC 27009**

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

1. **Active Ingredient(s):** atovaquone
2. **Strength(s):** 750mg atovaquone per 5ml
3. **Trade Name:** MEPRON
4. **Dosage Form:** Suspension
5. **NDA Number:** 20-500
6. **Approval Date:** February 8, 1995
7. **Applicable Patent Numbers and Expiration Date:**

Patent No.: 5,053,432

Expires: October 1, 2008

Orphan Drug No. 90-489

**MEPRON (atovaquone) for the Prevention of *Pneumocystis carinii*
Pneumonia**

Statement of Intention to Request Orphan Drug Marketing Exclusivity

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 MEPRON (atovaquone) Suspension for the prevention of *pneumocystis carinii* pneumonia.

This request will be based on the following information:

- The drug substance (atovaquone, MEPRON, 566C80) and indication (prevention of pneumocystis carinii pneumonia (PCP)) has previously been granted an Orphan Drug designation by the Office of Orphan Products Development on 14 August 1991.
- The specific wording of the indication is "566C80 qualifies for orphan designation for the prevention of *Pneumocystis carinii* pneumonia in high-risk, HIV-infected patients defined by one or both of the following criteria: (1) a history of one or more episodes of PCP, (2) a peripheral CD4⁺ (T helper/inducer) lymphocyte count less than or equal to 200/mm³."
- Inclusion criteria for both of the studies provided as the basis for substantial evidence of safety and efficacy for MEPRON Suspension for the prevention of PCP in this application required that patients must have had a previous episode of PCP (histologically confirmed), or have had a documented CD4⁺ lymphocyte count less of <200/mm³ or <20% of total lymphocytes with laboratory documentation of HIV infection.

EXCLUSIVITY SUMMARY for NDA # 20-500 SUPPL # S-005

Trade Name MEPRON® Generic Name atovaquone
Applicant Name Glaxo Wellcome Research and Development HFD-590

Approval Date January 5, 1999

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 questions 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?

3

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?

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).

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ON ORIGINAL

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 # 20-259 _____

NDA # 20-500 _____

NDA # _____

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 # _____

NDA # _____

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (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 / /

APPEARS THIS WAY
ON ORIGINAL

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:

Investigation #1, Study # 115-211

Investigation #2, Study # 115-213

Investigation #3, Study # _____

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ON ORIGINAL

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 / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /
Investigation #2	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /
Investigation #3	YES / <input type="checkbox"/> /	NO / <input type="checkbox"/> /

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

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

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 / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /
Investigation #2	YES / <input type="checkbox"/> /	NO / <input checked="" type="checkbox"/> /
Investigation #3	YES / <input type="checkbox"/> /	NO / <input type="checkbox"/> /

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

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

APPEARS THIS WAY
ON ORIGINAL

- 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"):

Investigation #_, Study # 115-211

Investigation #_, Study # 115-213

Investigation #_, Study # _____

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?

Investigation #1

YES /__ / Explain _____ NO /__ / Explain _____

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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: _____

 / S /

Signature _____
Title: Project Manager

04-Jan-99
Date

APPEARS THIS WAY
ON ORIGINAL

 / S /

Signature of Division Director

1/5/99
Date

APPEARS THIS WAY
ON ORIGINAL

cc: Original NDA

Division File HFD-85 Mary Ann Holovac

NDA 20-500

MEPRON (atovaquone) Suspension

Request for Marketing Exclusivity

Under Sections 505(c)(3)(D)(iii) and 505(j)(4)(D)(iii) of the Federal Food, Drug, and Cosmetic Act, Glaxo Wellcome Inc. requests three years of exclusivity from the date of approval of MEPRON (atovaquone) Suspension for the prevention of *pneumocystis carinii* pneumonia.

Glaxo Wellcome Inc. is entitled to such exclusivity as this application contains a report of a new clinical investigation (other than a bioavailability study) essential to the approval of the application and conducted or sponsored by Glaxo Wellcome Inc. This investigation is "essential to the approval of the application" in that the application could not be approved by FDA without the following investigation:

GW115-213 A Randomized, Open-Label Trial of High Dose Atovaquone vs Low Dose Atovaquone vs Aerosolized Pentamidine for Prophylaxis of *Pneumocystis carinii* Pneumonia in Patients with HIV Infection Who are Intolerant of TMP/SMX.

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 any such investigations.

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

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

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.

NDA/BLA # 20-500

Supplement # S-005

Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-590 Trade and generic names/dosage form: Mepron® (atovaquone)

Action: AP AE NA

Applicant Glaxo Wellcome, Inc.

Therapeutic Class Anti-parasitic

Indication(s) previously approved Treatment of *Pneumocystis carinii* pneumonia

Pediatric information in labeling of approved indication(s) is adequate inadequate

Indication proposed in this application Prophylaxis of *Pneumocystis carinii* pneumonia

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? Yes (Continue with questions) No (Sign and return the form)

IN WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

Neonates (Birth-1month) Infants (6months-2yrs) Children (2-12yrs) Adolescents(12-16yrs)

1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. 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 age groups. Further information is not required.

2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

3. 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. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

c. 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, attach memo describing status of discussions.

d. 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.

4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE 4 COMMITMENTS IN THE ACTION LETTER? Yes No
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Robert Hopkins, Medical Team Leader (e.g., medical review, medical officer, team leader)

/S/ Project Manager
Signature of Preparer and Title

January 5, 1999
Date

Orig NDA/BLA # 20-500
HFD-590/Div File
NDA/BLA Action Package
HFD-006/ KRoberts

FOR QUESTIONS ON COMPLETING THIS FORM, CONTACT KHYATI ROBERTS, HFD-6 (ROBERTSK)

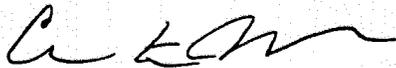
(revised 10/20/97)

Mepron (atovaquone) Suspension

NDA 20-500

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.



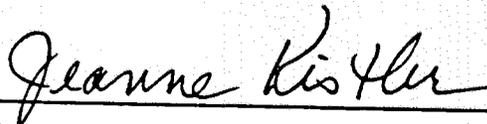
Charles E. Mueller
Head, International Compliance Services
World Wide Compliance

15 DEC 97

Date

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The list of Glaxo Wellcome Principal Investigators for the above titled submission has been compared with the 12Nov97 Food and Drug Administration Debarment List and the 22Aug97 Disqualified, Restricted, and Given Assurances lists.



Jeanne Kistler
Compliance Standards & Information Administrator
World Wide Compliance

15-Dec-97

Date



National Institutes of Health
Bethesda, Maryland 20892

Bldg: SOLAR
Room: 2B/06
(301) 496-8213

NDA 20-500
MEPRON (atovaquone) Suspension

DEBARMENT CERTIFICATION

The Division of AIDS, NIAID, NIH certifies that to the best of its knowledge and belief, it did not use in any capacity the services of any persons debarred under section 306(a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with the following protocol:

CPCRA 034/ACTG 277: A Randomized, Comparative Study of Daily Dapsone and Daily Atovaquone for Prophylaxis Against PCP in HIV-Infected Patients Who Are Intolerant of Trimethoprim and/or Sulfonamides

MSI
Signature
Mary Anne Luzar, Ph.D.
Chief, Regulatory Affairs Section
Pharmaceutical & Regulatory Affairs Branch
Division of Acquired Immunodeficiency Syndrome
National Institute of Allergy and Infectious Diseases

Sept. 30, 1997
Date



RECORD OF INDUSTRY MEETING

Meeting Date: September 24, 1997 Time: 10:00 Location: S400

NDA Number and Drug Name: 20-500 MEPRON® (atovaquone) suspension

External meeting requestor: GlaxoWellcome, Inc

Type of Meeting: Pre-SNDA

Meeting Chair: Marianne Mann, M.D. Sponsor Chair: Thomas K. Shumaker, M.S.

Project Manager: Brenda J. Atkins, Project Manager

FDA Attendees, Titles, and Offices:

Mark Goldberger, M.D., M.P.H., Director
Teresa Wu, M.D., Acting Clinical Team Leader
Joyce Korvick, M.D., Senior Medical Reviewer
Marianne Mann, M.D., Medical Officer
Norman Schmuff, Ph.D., Chemistry Team Leader
Aloka Chakravarty, Ph.D., Acting Statistical Team Leader
Funmilayo Ajayi, Ph.D., Acting Biopharmaceutics Team Leader
Kellie Reynolds, Ph.D., Biopharmaceutics Reviewer
Steven Kunder, Ph.D., Pharmacology Reviewer
Shukal Bala, Ph.D., Microbiology Reviewer
Brenda J. Atkins, Project Manager

External Constituent and Titles:

Michael Rogers, Ph.D., Associate Director, Antiviral Clinical Research
Thomas Shumaker, M.S., Manager, Regulatory Affairs
Mary Boshkoff, R.N., Regulatory Submissions Specialist
Paul Caldwell, Senior Scientist, Antiviral Clinical Research
David Cocchetto, Director, Regulatory Affairs
Denise Rasmus, Manager, CMC Regulatory Submissions
Brian Sadler, Ph.D., Clinical Pharmacokineticist, Clinical Pharmacology
Janna Scott, Senior Statistician
Joseph Woolley, Ph.D., Section Head, International Development Support

Background:

On August 5, 1997, the sponsor requested a pre-supplemental New Drug Application (pre-sNDA) meeting with FDA representatives in the Division of Special Pathogens and Immunologic Drug Products. In addition, the background meeting package was submitted concurrently with the request for a meeting. The meeting request was confirmed via facsimile dated September 3, 1997. An FDA internal meeting of September 19, 1997, raised issues/comments that were formulated into a facsimile and sent to the sponsor on September 19, 1997. These eleven issues/comments contained in the facsimile served as additional agenda items for discussion at the September 24, 1997, face-to-face meeting.

The sponsor is planning to submit a sNDA in accordance with 21 CFR Part 314.50 to their approved NDA 20-500 for MEPRON® (atovaquone) Suspension for the prophylaxis of *Pneumocystis carinii pneumonia* (PCP) with two adequate and well-controlled trials of MEPRON vs recognized standards-of-care for the prophylaxis of this disease and a CMC Technical Section to describe a new container/closure for the drug product proposed for the indication. The sNDA submission can be expected in the first quarter of 1998.

Meeting Objectives:

1. To determine if there is sufficient data on safety and effectiveness to allow a decision to be made for the indication of MEPRON® for the prophylaxis of PCP.
2. To obtain agreement on the contents of the submission as defined by the draft Table of Contents.
3. To determine if the stability protocol and submission requirements for the Drug Product, developed through prior discussion with the Division, and outlined in the Table of Contents, are acceptable to the Division.
4. To determine what other efficacy or safety analyses, beyond those described in Attachment 6, would the Division wish to see in the application.
5. To determine if the proposal to provide patient data listings and not case report tabulations is acceptable to the Division.
6. To determine if the proposal on submission of Case Report Forms, for deaths and discontinuations due to an adverse event (AE), is acceptable to the Division.
7. To determine if electronic versions of any documents or datasets will be required by the Division of its review.
8. To identify an estimated time for review of the sNDA.
9. To address issues/concerns in the September 19, 1997, facsimile.

Discussion/Item 1:

Sufficiency of data on safety and effectiveness

Decisions/Agreements Reached:

There is sufficient data on safety and effectiveness to allow an FDA decision to be made for the indication of MEPRON® for the prophylaxis of PCP.

Unresolved Issues or Issues Requiring Further Discussion:

None

Discussion/Item 2:

CMC

Decisions/Agreements Reached:

The CMC information on the 10mL unit dose sachet and the 5mL unit dose sachet will be filed concurrently in a sNDA submission later this year (November 1997). Draft labeling in this submission will only pertain to the 5mL unit dose sachet. Labeling for the 1500 mg, 10mL unit dose sachet will be filed as a chemistry supplement, i.e., as a package change supplement (SCP).

Unresolved Issues or Issues Requiring Further Discussion:

None

Discussion/Item 3:

Events following drug discontinuation

Decisions/Agreements Reached:

FDA will place most emphasis on those events (whether PCP, death, or adverse events) which occurred within 30 days of stopping study drug. Given the above, FDA made it clear that clinical follow up on all patients who discontinue study drug is necessary for at least 30 days. Every effort should be made to obtain 30-day follow up on all patients who stopped study drug. Information on the relative activity of dapsone for PCP prophylaxis would be very helpful to analyzing the CPCRA data. A complete analytical review of the GlaxoWellcome 213 study should include comparable analyses, (including 95% confidence intervals) as were performed for the CPCRA study.

Unresolved Issues or Issues Requiring Further Discussion:

None

Discussion/Item 4:

FDA's preferences on presentation of patient data

Decisions/Agreements Reached:

All case report forms (CRFs) will be electronically submitted along with patient data listings for GW115-213. For CPCRA 034, the sponsor will submit examples of electronically simulated CRFs vs. facsimile original CRFs for FDA to review. Once a format is decided upon, the sponsor will submit CRFs for the following:

1. All PCP confirmed or probable cases.
2. All patients who discontinue study drug and did not have at least 30 days follow up.
3. Ten percent of all deaths.
4. Ten percent of all discontinued due to adverse events.
5. Ten percent of a remaining random sample.

Unresolved Issues or Issues Requiring Further Discussion:

Upon receipt of the sample electronically simulated CRFs and the facsimile original CRFs, the FDA will notify the sponsor of its preferences.

Discussion/Items 5:

Format of electronic submissions

Decisions/Agreements Reached:

It was agreed that the sponsor would provide a clinical summary, labeling, and all texts/figures in a WORD format. The FDA requested that figures be placed appropriately within the text and the sponsor agreed. A SAS dataset will be submitted to the statistician. The statistician will provide guidance on what the FDA finds useful in SAS dataset submissions. ✓

Unresolved Issues or Issues Requiring Further Discussion:

None

Discussion/Item 6:

Review timeframe

Decisions/Agreements Reached:

The sNDA will be put on a 12-month review clock with hopes that it can be done sooner.

Unresolved Issues or Issues Requiring Further Discussion:

None

Discussion/Items 7:

Pediatric PK data

Decisions/Agreements Reached:

Pediatric PK data will be filed by the sponsor as either a part of the planned supplement for PCP prophylaxis or may be filed as a separate supplement. FDA agreed the information regarding pediatric dosing and tolerance is desirable; however, efficacy statements should be avoided. ✓

Unresolved Issues or Issues Requiring Further Discussion:

None

Discussion/Item 8:

Submission of preclinical carcinogenicity studies

Decisions/Agreements Reached:

Preclinical carcinogenicity studies do not need to be resubmitted with this sNDA.

Unresolved Issues or Issues Requiring Further Discussion:

None

Action/Follow-up Items:

1. FDA statistician will provide guidance on SAS dataset submissions. (Note: Guidance faxed on October 22, 1997.)
2. Upon receipt of the sample electronically simulated CRFs and the facsimile original CRFs, FDA will notify the sponsor of its preferences. (Note: Sponsor notified on October 8, 1997, that original CPCRA CRFs were preferred.)
3. The sponsor will provide an executive summary or a brief interpretation on MEPRON®'s superiority in treatment of PCP compared to Dapsone. Labeling should contain information about Dapsone, i.e, if on Dapsone, a patient should remain on Dapsone. ✓

- 4. Gastrointestinal intolerance among MEPRON® patients will receive more attention by the sponsor and additional wording may be added in the labeling to address the malabsorption issue.
- 5. A determination to file either the Environmental Assessment or the waiver request will be made before the clinical sNDA is submitted. ✓

Signature, minutes preparer: _____ /S/ _____ /s/10/24/97
Concurrence Chair: _____ /S/ _____ /s/

Attachments/Handouts

APPEARS THIS WAY
ON ORIGINAL