CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-078

ADMINISTRATIVE DOCUMENTS

NDA 21-078

PATENT INFORMATION FOR

MALARONE® (atovaquone and proguanil hydrochloride) Tablets

Patent Information on Product
of
Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

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

Trade Name: **MALARONE®**

Active Ingredient: Atovaquone and Proguanil Hydrochloride

Patent Number: 5,053,432

Expiration Date: October 1, 2008

Type of Patent: Drug Substance, Drug Product

Name of Patent Owner: Glaxo Wellcome Inc.

U.S. Agent:
David J. Levy, Ph.D.
Vice President and Patent Counsel
Glaxo Wellcome Inc.
5 Moore Drive
Research Triangle Park, North Carolina 27709

The undersigned declares that Patent No. 5,053,432 covers the composition, method of use and/or formulations of atovaquone. This product is the subject of this application for which approval is being sought.

Date: Dec. 7, 1998

By: Robert T. Hrubiec

Robert T. Hrubiec, Ph.D.
Intellectual Property Attorney
Glaxo Wellcome Inc.

EXCLUSIVITY SUMMARY FOR NDA # __21-078_____ SUPPL #_____

Trade Name _MALARONE_____ Generic Name **atovoquone/proguanil**

Applicant Name _Glaxo-Wellcome HFD # ___590_____

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /_X_/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /X__/

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

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 /_X_/ 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:

_____

_____

Form OGD-011347 Revised 10/13/98

cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

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

3 years

e) Has pediatric exclusivity been granted for this Active Moiety? **Not as of yet**

Pediatric Written request letter was issued December 10, 1998

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

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /_X_/

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 /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES /___/ NO /___/

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

NDA# _____ _____

NDA# _____ _____

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 /_X_/ NO /___/

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

NDA# __20-500_____ atovaquone suspension Mepron
Approved February 8, 1995

NDA# _____ _____

NOTE: NDA _____
This was never approved under FDNC Act as ammended in 1962.

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."

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**

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

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.

Explanation:

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:

Explanation:

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 years

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

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.

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

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Yes **No**

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).

Drug Product

NDA #

2. Combination product.

Yes No

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).

Drug Product atovaquone suspension Mepron

NDA # 20-500 Approved February 8, 1995

Drug Product

NDA #

NOTE: NDA

This product was never approved under FDNC Act as ammended in 1962.

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

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**

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCKS.

Basis for conclusion:

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:

TREATMENT INVESTIGATIONS

Investigation #1, Study #:Protocol 115-120: A Comparative Clinical Trial of a Combination of Atovaquone and Proguanil versus Chloroquine of Fansidar in the Treatment of Acute *P. falciparum* Malaria in Adults in Zambia

Investigation #2, Study #: Protocol 115-122: A Comparative Clinical Trial of a Combination of Atovaquone and Proguanil with Mefloquine in the Treatment of Acute *P. falciparum* Malaria in Adults in Thailand

Investigation #3, Study #: Protocol 115-127: A Comparative Clinical Trial of a Combination of Atovaquone and Proguanil versus a Combination of Quinine and Tetracycline in the Treatment of Acute *P. falciparum* Malaria in Adults in Brazil

Investigation #4, Study #: Protocol 115-130: A Comparative Clinical Trial of a Combination of Atovaquone and Proguanil versus Halofantrine in the Treatment of Acute *P. falciparum* Malaria in Non-Immune Adults in Europe

Investigation #5, Study#: Protocol 115-131: Comparative Clinical Trial of a Combination of Atovaquone and Proguanil versus Halofantrine in the Treatment of Acute *P. falciparum* Malaria in Children in Kenya

Investigation #6, Study#: Protocol 115-134: Comparative Clinical Trial of a Combination of Atovaquone and Proguanil versus Amodiaquine in the Treatment of Acute *P. falciparum* Malaria in Adults in Gabon

Investigation #7, Study: Protocol 115-135: Comparative Clinical Trial of a Combination of Atovaquone and Proguanil versus Chloroquine in the Treatment of Acute *P. falciparum* Malaria in Adults and Children in the Phillipines

Investigation #8, Study: Protocol 115-136: Comparative Clinical Trial of a Fixed Formulation of Atovaquone and Proguanil versus Chloroquine in the Treatment of Acute *P. falciparum* Malaria in Adults or Children in Peru

PROPHYLAXIS INVESTIGATIONS

Investigation #9, Study: Protocol MALB2001: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Determine the Chemosuppressive Activity of a Fixed Dose Combination of atovaquone/proguanil (Malarone) in Volunteers at Risk of Developing ~~*P. falciparum*~~ Malaria in Kenya

Investigation #10, Study: Protocol MALB3001: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Suppressive Prophylactic Activity of Malarone (atovaquone/proguanil) in Volunteers at Risk of Developing *P. falciparum* Malaria in Zambia

Investigation #11, Study: Protocol MALB3003: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Suppressive Prophylactic Activity of Malarone (atovaquone/proguanil) in Children at Risk of Developing *Plasmodium falciparum* Infection

Investigation #12, Study: Protocol MALB2002: A Randomized, Double-Blind, Placebo-Controlled Trial in Adult Volunteers in the US

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

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

Investigation # 1
Yes No

Investigation # 2
Yes No

Investigation # 3
Yes No

Investigation # 4
Yes No

Investigation # 5
Yes No

Investigation # 6
Yes No

Investigation # 7
Yes No

Investigation # 8
Yes No

Investigation # 9
Yes No

Investigation # 10
Yes No

Investigation # 11
Yes No

Investigation # 12
Yes No

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

Investigation #1 -- NDA Number
Investigation #2 -- NDA Number
Investigation #3 -- NDA Number

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

Investigation # 1
Yes No

Investigation # 2
Yes No

Investigation # 3
Yes No

Investigation # 4
Yes No

Investigation # 5
Yes No

Investigation # 6
Yes No

Investigation # 7
Yes No

Investigation # 8
Yes No

Investigation # 9
Yes No

Investigation # 10
Yes No

Investigation # 11
Yes No

Investigation # 12
Yes No

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

Investigation #1 -- NDA Number
Investigation #2 -- NDA Number

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"):

TREATMENT INVESTIGATIONS

Investigation #1, Study #:Protocol 115-120: A Comparative Clinical Trial of a Combination of Atovaquone and Proguanil versus Chloroquine of Fansidar in the Treatment of Acute *P. falciparum* Malaria in Adults in Zambia

Investigation #2, Study #: Protocol 115-122: A Comparative Clinical Trial of a Combination of Atovaquone and Proguanil with Mefloquine in the Treatment of Acute *P. falciparum* Malaria in Adults in Thailand

Investigation #3, Study #: Protocol 115-127: A Comparative Clinical Trial of a Combination of Atovaquone and Proguanil versus a Combination of Quinine and Tetracycline in the Treatment of Acute *P. falciparum* Malaria in Adults in Brazil

Investigation #4, Study #: Protocol 115-130: A Comparative Clinical Trial of a Combination of Atovaquone and Proguanil versus Halofantrine in the Treatment of Acute *P. falciparum* Malaria in Non-Immune Adults in Europe

Investigation #5, Study#: Protocol 115-131: Comparative Clinical Trial of a Combination of Atovaquone and Proguanil versus Halofantrine in the Treatment of Acute *P. falciparum* Malaria in Children in Kenya

Investigation #6, Study#: Protocol 115-134: Comparative Clinical Trial of a Combination of Atovaquone and Proguanil versus Amodiaquine in the Treatment of Acute *P. falciparum* Malaria in Adults in Gabon

Investigation #7, Study: Protocol 115-135: Comparative Clinical Trial of a Combination of Atovaquone and Proguanil versus Chloroquine in the Treatment of Acute *P. falciparum* Malaria in Adults and Children in the Phillipines

Investigation #8, Study: Protocol 115-136: Comparative Clinical Trial of a Fixed Formulation of Atovaquone and Proguanil versus Chloroquine in the Treatment of Acute *P. falciparum* Malaria in Adults or Children in Peru

PROPHYLAXIS INVESTIGATIONS

Investigation #9, Study: Protocol MALB2001: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Determine the Chemosuppressive Activity of a Fixed Dose Combination of atovaquone/proguanil (Malarone) in Volunteers at Risk of Developing *P. falciparum* Malaria in Kenya

Investigation #10, Study: Protocol MALB3001: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Suppressive Prophylactic Activity of Malarone (atovaquone/proguanil) in Volunteers at Risk of Developing *P. falciparum* Malaria in Zambia

Investigation #11, Study: Protocol MALB3003: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Suppressive Prophylactic Activity of Malarone (atovaquone/proguanil) in Children at Risk of Developing *Plasmodium falciparum* Infection

Investigation #12, Study: Protocol MALB2002: A Randomized, Double-Blind, Placebo-Controlled Trial in Adult Volunteers in the US

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

Investigation # 2
IND — Yes No

Investigation # 3
IND — Yes No

Investigation # 4
IND — Yes No

Investigation # 5
IND — Yes No

Investigation # 6
IND — Yes No

Investigation # 7
IND — Yes No

Investigation # 8
IND — Yes No

Investigation # 9
IND — Yes No

Investigation # 10
IND — Yes No

Investigation # 11
IND — Yes No

Investigation # 12
IND — Yes No

b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

N/A because the Applicant was identified as the sponsor in the IND.

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

6/15/99
Date

/S/
Signature of Office Director

6/30/99
Date

cc:

Original NDADivision FileHFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: N 021078
Trade Name: MALARONE (ATOVAQUONE/PROGUANIL HCL) TABL
Generic Name: ATOVAQUONE/PROGUANIL HCL
Supplement Number: 000 **Supplement Type:** N
Dosage Form:
Regulatory Action: AP **Action Date:** 7/14/00
COMIS Indication: TREATMENT AND PREVENTION OF MALARIA

Indication #1 Treatment and prophylaxis of P. falciparum malaria.
Label Adequacy: Adequate for some pediatric age groups
Formulation Needed: Other
Comments (if any) Information requested to possibly result in labeling for pediatric patients unable to swallow a whole tablet. Efficacy study currently underway using crushed Malarone Pediatric tablets.

Lower Range	Upper Range	Status	Date
5 kg	11 kg	Deferred	4/1/02
0 kg	5 kg	Waived	

This page was last edited on 11/12/00

Signature

Date 1/18/01

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21078	**Trade Name:**	MALARONE (ATOVAQUONE/PROGUANIL HCL) TABL
Supplement Number:		**Generic Name:**	ATOVAQUONE/PROGUANIL HCL
Supplement Type:		**Dosage Form:**	Tablet; Oral
Regulatory Action:	AE	**Proposed Indication:**	Treatment and prophylaxis of P. falciparum malaria.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?
YES, Pediatric data exists for at least one proposed indication which supports pediatric approval

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days)
____Infants (1-24 Months)
____Children (25 Months-12 years)
_X_Adolescents (13-16 Years)
_X_Other Age Groups (listed): above 3 yrs

Label Adequacy	Adequate for SOME pediatric age groups
Formulation Status	NEW FORMULATION needed, Applicant has AGREED to provide it
Studies Needed	No further STUDIES are needed
Study Status	Protocols are submitted and approved

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? YES

COMMENTS:
Glaxo agreed in the Pediatric Written Request of December 10, 1998, to determine the bioavailabliity of a suitable dosing form that can be taken by patients who can not swallow tablets..

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, MARY DEMPSEY

[signature] _____ 6/28/99

Signature **Date**

12/11/00

To: NDA 21-078, Malarone™ tablets for malaria treatment and prophylaxis

From: Andrea Meyerhoff, M.D., M.Sc., D.T.M.H., Medical Officer, Division of Special Pathogen and Immunologic Drug Products

Subject: Partial Waiver of Pediatric Use Requirement

Glaxo Wellcome Inc. has fulfilled the pediatric study requirements for NDA 21-078 for pediatric patients weighing greater than or equal to eleven kilograms.

The Division of Special Pathogen and Immunologic Drug Products agreed to defer submission of pediatric study reports for pediatric patients weighing less than eleven kilograms and greater than or equal to five kilograms until April 1, 2002 for NDA 21-078. Glaxo Wellcome Inc. submitted a Proposed Pediatric Study Request dated June 8, 2000 which proposes two pediatric studies for treatment of *Plasmodium falciparum* malaria in pediatric patients weighing less than eleven kilograms and greater than or equal to five kilograms.

The risk of exposing pediatric patients weighing less than five kilograms to malaria for the prophylaxis indication would not be justifiable. Malarone™ would not be likely to be used for either malaria prophylaxis or treatment in a substantial number of U.S. pediatric patients in this weight range. For these reasons, the Division agrees to grant a waiver for the pediatric study requirement for pediatric patients weighing less than five kilograms for NDA 21-078.

NDA 21-078

MALARONE™ (atovaquone and proguanil hydrocloride) Tablets
Treatment and Prevention of Malaria

DEBARMENT CERTIFICATION

Glaxo Wellcome hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

	9 DEC 98
Charles E. Mueller	Date
Head, Clinical Compliance	
World Wide Compliance	

OFFICES OF DRUG EVALUATION
ORIGINAL NDA/NDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST

NDA # 21-078 Drug MALARONE DATE 6/16/99

Applicant GLAXO WELLCOME CSO MARY DEMPSEY Phone 7-2127

User Fee Goal Date: JUNE 30, 1999

Arrange package in the following order:	Check or Comment
1. ACTION LETTER with supervisory signatures Are there any Phase 4 commitments?	AP ____ AE ✓ NA ____ Yes ✓ No ____
2. Have all disciplines completed their reviews? If no, what review(s) is/are still pending?	Yes ✓ No ____
3. Completed copy of this CHECKLIST in package	Chem/Ther Types HP
4. LABELING (package insert and carton and container labels). (If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.)	Draft ✓ Revised Draft N/A Final N/A
5. PATENT INFORMATION	✓
6. EXCLUSIVITY CHECKLIST	✓
7. PEDIATRIC PAGE	✓
8. DEBARMENT CERTIFICATION (Copy of applicant's certification for all NDAs submitted on or after June 1, 1992).	✓
9. Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status. If no audits were requested, include a memo expaining why.	✓
10. REVIEWS:	
DIVISION DIRECTOR'S MEMO (If more than 1 review for any discipline, separate reviews with a sheet of colored paper. Any conflicts between reviews must have resolution documented)	N/A
GROUP LEADER'S MEMO	✓
MEDICAL REVIEW	✓
SAFETY UPDATE REVIEW	N/MC Review
STATISTICAL REVIEW	✓
BIOPHARMACEUTICS REVIEW	✓
PHARMACOLOGY REVIEW (Include pertinent IND reviews)	✓
Statistical Review of Carcinogenicity Study(ies)	N/A
CAC Report/Minutes	N/A
CHEMISTRY REVIEW	✓
Labeling and Nomenclature Committee Review Memorandum	✓
Date EER completed ___ (attach signed form or CIRTS printout) FUR needed N/A FUR requested ____	OK ✓ No ____
Have the methods been validated?	Yes (attach) ____ No ✓
Environmental Assessment Review / FONSI	Review N/A FONSI N/A
MICROBIOLOGY REVIEW	✓
What is the status of the monograph?	
11. CORRESPONDENCE, MEMORANDA OF TELECONS, and FAXes	✓
12. MINUTES OF MEETINGS Date of End-of-Phase 2 Meeting N/A Date of pre-NDA Meeting ✓ 9/10/97	✓
13. ADVISORY COMMITTEE MEETING MINUTES or, if not available, 48-Hour Info Alert or pertinent section of transcript.	Minutes ____ Info Alert ____ Transcript ____ No mtg ✓
14. FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS	N/A
15. If approval letter, has ADVERTISING MATERIAL been reviewed? If no and this is an AP with draft labeling letter, has advertising material already been requested?	Yes ____ No ✓ Yes, documentation attached ____ No, included in AP ltr ✓ AE

revision 3/7/96

CONTINUE TO NEXT PAGE

ACTION PACKAGE CHECKLIST

16.	INTEGRATED SUMMARY OF EFFECTIVENESS	N/A
17.	INTEGRATED SUMMARY OF SAFETY	N/A

revision: 3/7/96

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-078 Drug Malarone (atovaquone/proguanil) Applicant Glaxo Wellcome

RPM Valerie Jensen Phone 301 827-2374

☒ 505(b)(1)
☐ 505(b)(2) Reference listed drug _____

☐ Fast Track ☐ Rolling Review ☐ Class I (Resubmission) ☒ Class II Review priority: ☐ S ☒ P

Pivotal IND(s) ___

Application classifications:
Chem Class 4P
Other (e.g., orphan, OTC) _____

PDUFA Goal Dates:
Primary July 21, 2000
Sedondary _____

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

◆ User Fee Information ..... ☐ User Fee Waiver (attach waiver notification letter) ☐ User Fee Exemption

◆ Action Letter ..... ☒ AP ☐ AE ☐ NA

◆ Labeling & Labels
- FDA revised labeling and reviews X
- Original proposed labeling (package insert, patient package insert) X
- Other labeling in class (most recent 3) or class labeling ..... N/A
- Has DDMAC reviewed the labeling? ..... ☐ Yes (include review) ☒ No
- Immediate container and carton labels X
- Nomenclature review X

◆ Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ☒ is not on the AIP
- Exception for review (Center Director's memo) ..... N/A
- OC Clearance for approval ..... N/A

◆ Status of advertising (if AP action) .. ☐ Reviewed (for Subpart H- attach review) ☒ Materials requested in AP letter

◆ Post-marketing Commitments
- Agency request for Phase 4 Commitments X
- Copy of Applicant's commitments (in AP letter) X

◆ Was Press Office notified of action (for approval action only)? ..... ☒ Yes ☐ No
- Copy of Press Release or Talk Paper X

Continued ⇨

◆ Patent
Information (505(b)(1)) X
Patent Certification (505(b)(2)) ..... N/A
Copy of notification to patent holder (21 CFR 314.50 (i)(4)) X

◆ Exclusivity Summary X

◆ Debarment Statement X

◆ Financial Disclosure N/A original submission prior to 2/2/99
No disclosable information ..... N/A
Disclosable information – indicate where review is located ..... N/A

◆ Correspondence/Memoranda/Faxes X

◆ Minutes of Meetings X
Date of EOP2 Meeting N/A
Date of pre NDA Meeting 9/10/97
Date of pre-AP Safety Conference 4/18/00

◆ Advisory Committee Meeting ..... N/A
Date of Meeting N/A
Questions considered by the committee ..... N/A
Minutes or 48-hour alert or pertinent section of transcript ..... N/A

◆ Federal Register Notices, DESI documents ..... N/A

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) X

◆ Clinical review(s) and memoranda X

◆ Safety Update review(s) (incorporated into review) X

◆ Pediatric Information X
☒ Waiver/partial waiver (Indicate location of rationale for waiver) ☒ Deferred
Pediatric Page (AP letter) Rationale located under Pediatric Page X

◆ Statistical review(s) and memoranda X

◆ Biopharmaceutical review(s) and memoranda X

Continued ⇨

◆ Abuse Liability review(s) ..... N/A.
Recommendation for scheduling ..... N/A.

◆ Microbiology (efficacy) review(s) and memoranda X

◆ DSI Audits X
☒ Clinical studies ☐ bioequivalence studies

CMC INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

◆ CMC review(s) and memoranda (Team Leader's memo) X

◆ Statistics review(s) and memoranda regarding dissolution and/or stability ..... N/A

◆ DMF review(s) X

◆ Environmental Assessment review/FONSI/Categorical exemption X

◆ Micro (validation of sterilization) review(s) and memoranda ..... N/A

◆ Facilities Inspection (include EES report)
Date completed May 19, 2000 ..... ☒ Acceptable ☐ Not Acceptable

◆ Methods Validation ..... ☒ Completed ☐ Not Completed

PRECLINICAL PHARM/TOX INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

◆ Pharm/Tox review(s) and memoranda X

◆ Memo from DSI regarding GLP inspection (if any) ..... N/A

◆ Statistical review(s) of carcinogenicity studies ..... N/A

◆ CAC/ECAC report ..... N/A

K1.1

K1.1

N21078

N21078

NDA 21-078

RFC
1/22/01
T.52PM

MALARONE™

(atovaquone and proguanil)

Tablets

Glaxo Wellcome, Inc.
Stamp date: December 30, 1998
PDUFA date: June 30, 1999
Action date: June 30, 1999 (AE)
Class II resubmission: January 21, 2000
PDUFA date: July 21, 2000

Reviewed by the HAT TEAM: HFD-590
Medical TL/Robert Hopkins/Andrea Meyerhoff/Rigoberta Roca
Medical Officer/Andrea Meyerhoff
Medical Officer/Leonard Sacks
Chemist/John Smith
Pharmacologist/toxicologist/Steve Kunder
Biopharmaceutics Reviewer/Houda Mahayni
Microbiologist/Shukal Bala
Statistical Reviewer/Joel Jiang
Project Manager/Mary Dempsey/Valerie Je

CAROL
DOYLE

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. *0910-0297*
Expiration Date: *November 30, 1996.*

USER FEE COVER SHEET

See Instructions on Reverse Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

2. USER FEE BILLING NAME, ADDRESS, AND CONTACT

E. Allen Jones, Regulatory Affairs
Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709
Telephone (919) 483-9122

3. TELEPHONE NUMBER *(Include Area Code)* (919) 483-2100

4. PRODUCT NAME

MALARONE™ (atovaquone and proguanil hydrochloride) Tablets

5. DOES THIS APPLICATION CONTAIN CLINICAL DATA? ■ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

6. USER FEE I.D. NUMBER
3622

7. LICENSE NUMBER / NDA NUMBER
21-078

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 9/1/92

☐ THE APPLICATION IS SUBMITTED UNDER 505 (b)(2) *(See reverse before checking box.)*

☐ AN INSULIN PRODUCT SUBMITTED UNDER 506

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT

9 a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION? ☐ YES *(See reverse if answered YES)* ■ NO

b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES *(See reverse if answered YES)* ■ NO

This completed form must be signed and accompany each new drug or biologic product, original or supplement

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Thomas K. Shumaker	Thomas K. Shumaker Project Director Regulatory Affairs	December 22, 1998

Form FDA 3397 (12/93)

GlaxoWellcome

December 22, 1998

Mellon Bank
Food and Drug Administration
Three Mellon Bank Center
27th Floor (FDA 360909)
Pittsburgh, PA 15259-0001

Re: NDA 21-078; MALARONE™ (atovaquone and proguanil hydrochloride) Tablets for the Treatment and Prevention of Malaria
User Fee: With Clinical Data
User Fee # 3622

Please find enclosed Glaxo Wellcome check number # 1492889 in the amount of $256,846.00. This payment is 100% of the application fee for the New Drug Application for Malarone™ Tablets for treatment and prevention of Malaria.

This application will be submitted to the Center for Drug Evaluation and Research, FDA, by the end of December 1998.

Please find below requested information regarding this application

Type of Application:	New Drug Application with Clinical Data	X
	New Drug Application without Clinical Data	
	Supplemental New Drug Application with Clinical Data	

Should you have any questions, please contact me at (919) 483-9324. Thank you.

Sincerely,

Thomas K. Shumaker
Project Director,
Regulatory Affairs

Glaxo Wellcome Inc.
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

Telephone
919 248 2100

WITHHELD 1 PAGE(S)

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT #	HFD#	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
1145	590	Malarone	atovaquone and proguanil HCl
ATTENTION:	John Smith		

A. Look-alike/Sound-alike

	Potential for confusion:		
Milrinone	___ Low	___ Medium	XXX High
Mellaril	xxx Low	___ Medium	___ High
	___ Low	___ Medium	___ High
	___ Low	___ Medium	___ High
	___ Low	___ Medium	___ High

B. Misleading Aspects:

C. Other Concerns:

D. Established Name

xxx Satisfactory

___ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

___ ACCEPTABLE XXX UNACCEPTABLE

F. Signature of Chair/Date 5/1

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STATE OF NORTH CAROLINA

Department of The Secretary of State

I, **JANICE H. FAULKNER**, Secretary of State of the State of North Carolina, do hereby certify that the following is a listing of all changes in the corporate name of the corporation named below, insofar as disclosed by the records of this office:

Original name at date of incorporation or authorization:

BURROUGHS WELLCOME CO.

State of Incorporation: NC

Date of Incorporation or Authorization: 18 Aug 1970

Name Changes

Name change was effected by

Document and date filed or issued:	Name changed to:
Articles of Amendment filed 31 Oct 1995	**GLAXO WELLCOME INC.**

I **FURTHER CERTIFY** that this certificate is in compliance with North Carolina General Statutes §55-4-05 and may be recorded in the office of the Register of Deeds in the same manner as deeds, the former name of the corporation appearing in the "Grantor" index and the amended name of the corporation appearing in the "Grantee" index.

IN WITNESS WHEREOF, *I have hereunto set my hand and affixed my official seal at the City of Raleigh, this 27th day of September, 1996.*

Janice H. Faulkner

Secretary of State

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT # 1145	HFD# 590	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
ATTENTION: John Smith		Malarone	atovaquone and proguanil HCl

A. Look-alike/Sound-alike

	Potential for confusion:
Milrinone	___ Low ___ Medium XXX High
Mellaril	xxx Low ___ Medium ___ High
	___ Low ___ Medium ___ High
	___ Low ___ Medium ___ High
	___ Low ___ Medium ___ High

B. Misleading Aspects:

C. Other Concerns:

D. Established Name

xxx Satisfactory

___ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

___ ACCEPTABLE XXX UNACCEPTABLE

F. Signature of Chair/Date GT

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM

DATE: March 30, 1999

TO:

FROM: Mary Dempsey, Regulatory Project Manager

THROUGH: John Smith, Ph.D., Chemist

SUBJECT: DMF

Comments on DMF

1. The DMF conveys an impression that the manufacturing processes and analytical procedures described therein are still under development. For example:

If it has not already been done, please finalize the processes and procedures, and then amend the DMF as necessary so that the finalized processes and procedures and those described in the DMF are the same. In particular:

a.

b.

WITHHOLD 2 PAGE (S)

DMF

10. [redacted]

Please address these DMF issues as soon as possible. Should you need clarification on any of these comments, a telecon will be provided. Please contact Mary Dempsey, Regulatory Project Manager, at 301-827-2127.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Mary Dempsey
Regulatory Project Manager
Division of Special Pathogen and Immunologic Drug Products

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM

FEB 1 3

TO: Tom Shumaker, Regulatory

FROM: Mary Dempsey, Project Manager

THROUGH: Shukal Bala, Ph.D., Microbiologist, Act. Team Leader
John Smith, Ph.D., Chemist

DRUG: Malarone (atovaquone and proguanil)

NDA: 21-078

INDICATION: Treatment and prophylaxis of *P.* falciparum malaria.

Related Documents: N-000

SUBJECT: Chemistry and Microbiology Information request

The Microbiologist has requested the following information:

Lines 143 - 149 of the annotated package insert (proposed by the company) states the [redacted] However, no cross-references are cited.

Please provide exactly where that information is located in the NDA. Also please provide the basis of the information. References would be appreciated.

The Chemist has requested that you please provide us with your USAN plans.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

Mary Dempsey
Project Manager
Division of Special Pathogen and Immunologic Drug Products

45 DAY FILING MEETING CHECKLIST

February 11, 1999

NDA 21-078
Drug Name: Malarone (atovaquone and proguanil)
Dosage: 250 mg atovaquone/100 mg proguanil
62.5 mg atovaquone/25 mg progaunil
Indication: Treatment and prophylaxis of *P.falciparum* malaria.
Applicant: Glaxo Wellcome
Chemistry Type: 4P
Stamp date: December 30, 1998
Filing Date: March 1, 1999
OVEIV Goal Date: June 17, 1999
PDUFA Goal Date: June 30, 1999

FILEABILITY:

On initial overview of the NDA application:

PROJECT MANAGEMENT:

(1) Do any of the following apply to this application (i.e., if YES , the application MUST BE REFUSED TO FILE under 314.101 (e) and there is no filing over protest):

(a) Is the drug product already covered by an approved application?
Researching the regulatory history of NDA 6-453 (proguanil) one of the components of this NDA.

(b) Does the submission purport to be an abbreviated application under 314.55; however the drug product is not one for which FDA has made a finding that an abbreviated application is acceptable under 314.55(b)?
NO

c) Is the drug product subject to licensing by FDA under the Public Service Act and Subchapter F of Chapter I of Title 21 of the CFR?
NO

(2) Do any of the following apply to this application (i.e., if NO, the application MAY BE REFUSED TO FILE under 314.101(d) and there is the potential for filing over protest):

(a) Does the application contain a completed application form as required under 314.50 or 314.55? YES

(b) On its face, does the application contain the sections of an application required by regulation and Center guidelines?
- Clinical
- Biopharm
- Chemistry
- Pharm/Tox
- Statistics

YES

C) Has the applicant submitted a complete environmental assessment which addresses each of the items specified in the applicable format under 25.31 or has the applicant submitted evidence to establish that the product is under 25.24 of the CFR?

YES

(d) On its face, is the NDA formatted in compliance with Center guidelines including integrated efficacy and safety summaries? YES

(e) Is the NDA indexed and paginated? YES

(f) On its face, is the NDA legible? YES

(g) Has the applicant submitted all required copies of the submission and various sections of the submission? YES

(h) Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor? YES

(I) Does the application contain a statement that all nonclinical laboratory studies were conducted in compliance with the requirements set forth in Part 58 or a statement why a study was not conducted in compliance with those requirements? YES

(j) If required, has the applicant submitted carcinogenicity studies?

YES

(k) On its face, does the application contain at least two adequate and well-controlled clinical trials?

YES

(l) Does the application contain a statement that all clinical trials were conducted in accord with the IRB/Declaration of Helsinki provisions of the CFR?
YES

(m) Have all articles/study reports been submitted whether in English or translated into English?
YES

(n) Has the applicant submitted draft labeling in compliance with 210.56 and 210.57 of the CFR? YES

(o) Has the applicant submitted the required FRAUD POLICY notice?
YES

(p) Has the applicant submitted copies of all package inserts (or their equivalent) from all countries in which this product has been previously approved for marketing? Have all non-English package inserts been translated?
YES

(q) Has the applicant stated that the integrated summary of safety includes all safety data for this product of which they are aware from all sources, domestic and foreign? What is the cut-off date for the preparation of the ISS?
YES Cut-off date

(r) If this is a CANDA submission, has the applicant submitted a statement to the archival NDA that the text, tables, and data in the CANDA and the archival hard copy NDA are identical? If they are not identical, is there a letter to the archival NDA that specifies distinctly ALL of the differences in the two submissions? YES

(3) From a project management perspective, is this NDA fileable? If "no". please state on the reverse why it is not. YES

Project Manager

Supervisory Project Manager

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM

DATE: January 26, 1999

TO: Ton Shumaker, Regulatory Affairs

FROM: Mary Dempsey, Project Manager

THROUGH: Andrea Meyerhoff, M.D., M.Sc., DTMH, Medical Officer

APPLICANT: Glaxo Wellcome

NDA: 21-078

INDICATION: Treatment and prophylaxis of *Plasmodium falciparum* malaria.

Related Documents: Original NDA submission

SUBJECT: Information request

We received your NDA submission, NDA 21-078, for Malarone. In order to facilitate the review process, we request that you provide the following information. Please provide this information as submissions to your Malarone application.

1. Please provide a copy of the Case Report Forms and the Case Report Tabulations.

2. Please provide on diskettes the following:
   a) proposed label
   b) Item 3 summary
   c) ISSs and ISEs (a separate ISE for each indication and a separate ISS for each indication),
   d) text and tables for all phase II and III pivotal treatment and prophylaxis trials.

3. Please provide the following five papers for our review. They are listed according to the numbers of the volumes in which they can be found.

   a) vol 23, p26: Canfield et al (1995), Experimental Parasit 80:373-81

   b) vol 23, p 64: Findlay (1951) Recent advances in chemotherapy pp. 121-186

   c) vol 23, p176: Hill (1963)Exptl Chemotherapy pp.513, 552-563, 582-601

d) vol 34, p102: Foote and Cowman (1994) Acta Tropica 56:157-71

e) vol 34, p153: Peters (1990) Pharmacological Therapeutics 47:499-508

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

LS

Mary Dempsey
Project Manager
Division of Special Pathogens and Immunologic Drug Products

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM

TO: Tom Shumaker, Regulatory Affairs

FROM: Mary Dempsey, Project Manager

THROUGH: John Smith, Ph.D., Chemist

APPLICANT: Glaxo Wellcome

NDA: 21-078

DRUG: Malarone (atovaquone and proguanil hydrochloride) Tablets

1. Please examine the attached list of sites. Please confirm:
   (a) that each of the listed sites will be involved in the production of the drug product (or drug substance), or was involved in the manufacture or testing of batches described in NDA 21-078;
   (b) that there are no additional sites that should on the list (see comment below);
   (c) that the functions listed for each site are correct;
   (d) that the addresses are correct;
   (e) that the CFNs and DMF numbers are correct; and
   (f) that all facilities listed are ready for prior approval inspection.

Also, please provide any missing CFNs of DMF numbers, as appropriate.

2. Please provide the manufacturing locations and DMF references (if any) for the drug substance atovaquone.

NDA 21-078

Contact for pre-approval inspections: Dr. Ron Bobbie 919-269-1729

[redacted] CFN [redacted] DMF [redacted]

[redacted]

[redacted]

Role: [redacted]

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We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me if you have any questions regarding the contents of this transmission.

CSI

Mary Dempsey
Project Manage.
Division of Special Pathogens and Immunologic Drug Products

MEMORANDUM OF PRE-NDA MEETING
Malarone (atovaquone and proguanil hydrochloride)
tablets (IND)
September 10, 1997

PARTICIPANTS:

FDA/Division of Special Pathogens and Immunologic Drug Products:
Mark Goldberger, M.D., M.P.H. Division Director
Renata Albrecht, M.D., Deputy Division Director
Marc Cavaille Coll, M.D., Acting Team Leader, Clinical
Andrea Meyerhoff, M.D.,M.Sc., DTMH, Medical Officer
Phillip Coyne, M.D., M.P.H., Medical Officer
Kenneth Hastings, Ph.D., Team Leader, Pharmacology
Steve Kunder, Ph.D., Pharmacologist
Nancy Silliman, Ph.D., Biostatistician
Shukal Bala, Ph.D., Microbiologist
Kellie Reynolds, Ph.D., Biopharmacokenetic
Pauline Fogarty, Project Manager

Glaxo Wellcome:
Jeffrey Chulay, MD, DTM&H, Project Leader/MedicalAdvisor, Antiviral Clinical Research.
Trevor Scott, PhD, Medical Project Group Leader, Antiviral Clinical Research
Trupti Trivedi, Senior Statistician,
Ian Buxton, BSC, MRPharmS , Team Manager, Pharmaceutics,
Joseph Woolley, PhD, Section Head, International Development Support
Anton Zeman, Group Toxicologist, Medicine Safety Evaluation
Brian Sadler, PhD, Clinical Pharmacokineticist, Clinical Pharmacology
David Cocchetto, PhD, Director, Regulatory Affairs,
Vicky Jones, Chemistry and Pharmacy Regulatory Submissions
Kimberley Crippen, CMC Regulatory Submissions
Mary Boshkoff, RN, Regulatory Submissions Specialist
Thomas Shumaker, MS, Manager, Regulatory Affairs

After introductions, Glaxo Wellcome presented their plans for their pending NDA submission, with outline of Malarone for treatment and prophylaxis of malaria. (overheads attached). Open discussion then followed.

FDA/DSPIDP and Glaxo Wellcome agreed to the following:

1. That there should be information in the labeling about taking Malarone with fatty meal/drink for optimal absorption of the drug.

2. That available data on any resistant strains of microorganisms will be included in the NDA submission.

3. It would be necessary to know the limit on lifetime exposure of Malarone to adequately discuss the issue of carcinogenicity. This information should be a part of the NDA.

4. To use a hypothesis testing approach in all studies for the prophylaxis trials, (this was done for two studies, and will be added for the third study).

DSPIDP Recommendations and agreements:

1. That Reproductive Toxicology studies (segments 1 and 3) should be conducted. Since the sponsor has no plans to conduct these studies, but to refer to data from the approved drug MEPRON to support atovaquone and to refer to literature citations for proguanil, further internal discussion will be conducted followed by a telecon with Glaxo Wellcome in the near future.

2. That there needs to be carcinogenicity studies if prolonged use of Malarone is anticipated (>6 months). However with agreement this could be a phase IV commitment.

3. Although the data submitted demonstrate clear advantage of the use of the combination of atovaquone and proguanil compared with the use of atovaquone alone or of proguanil alone in the treatment of malaria, there is no documentation of similar advantage in prophylaxis. It is necessary that this be addressed. Citations from the published medical literature as well as prospective trial data would be acceptable.

4. The studies excluded patients with severe/complicated malaria, or with a parasite count of 200,000/ul. Further discussion will be needed in order to refine the population studied to properly write the labeling.

5. Although the results of the causal prophylaxis trial are encouraging, there is concern about the small number of patients (n=6) on which a recommendation of 7 days terminal prophylaxis would be based. Therefore, additional supporting data in the from of human or animal studies would be helpful.

6. This submission would qualify for a 6 month review. For this reason, electronic submissions of integrated efficacy and safety summaries, application summary, study reports, and draft

label would be helpful. Similarly submission of CRTs as well as line listings is preferred.

7. In preparing the NDA submission, it would be helpful to present results for subgroups such as women and children in the Integrated Summaries of Efficacy and Safety, and to have electronic versions of any final study reports and datasets (for pivotal clinical studies). Word and SAS are suggested, but electronic submissions in other formats would be acceptable.

8. For the treatment trials, an intention-to-treat analysis should be performed as a secondary analysis and missing data should be estimated as failures in this analysis. Also, for the treatment trials, we ask that results be displayed using confidence intervals (these are all active-control, equivalence).

9. The prophylaxis trials should be adjusted for multiple comparisons when the studies include each of a placebo, a low dose, and a high dose arm.

10. To address the issue of whether any head-to-head comparisons of dual versus single therapy exist, the Sponsor was asked to clarify whether any of their treatment trials concurrently randomized patients to atovaquone plus proguanil, atovaquone alone, or proguanil alone. The sponsor stated that no patients were concurrently randomized (i.e., there is no head-to-head comparative experience).

Unresolved Issues:

The discussion of CMC issues was deferred since there was no representation from the Division. A telecon will be arranged to discuss issues relating to the CMC part of the submission. Also, additional telecons to discuss pharm/tox; and formatting of CRTs in the near future.

LT

Pauline Fogarty
Project Manager

LT

Andrea Meyerhoff, M.D., M.Sc., D.T.M.H.
Chairperson

ATTACHMENT (overhead)

orig:cc
IND
Division File:
HFD-590/Goldberger
HFD-590/Albrecht
HFD-590/Cavaille-Coll
HFD-590/Meyerhoff
HFD-590/Coyne
HFD-590/Hastings
HFD-590/Kunder
HFD-590/Silliman
HFD-590/Bala
HFD-590/Reynolds
HFD-591/Fogarty
kk/10-23-97
MINUTES

Global Malaria Threat

- >2 billion persons at risk
- >200 million clinical cases per year
- >1 million deaths per year
- Drug resistance increasing

Impact of Malaria for US Citizens

- >1 million travelers at risk annually
- ~1,000 cases annually in returning travelers
- Available antimalarial drugs not optimal

Antimalarial Activity of Atovaquone

- Inhibits mitochondrial electron transport
- Potent *in vitro* inhibition of *P. falciparum* (IC_{50} = 0.7 - 4.3 nM)
- Efficacy in *Aotus* model of *P. falciparum*
- Active as causal prophylactic

Clinical Characteristics of Atovaquone

- Efficacy
  - 750 mg 3 x daily (tablet) or 750 mg 2 x daily (suspension) for 21 days effective for *Pneumocystis carinii* pneumonia
- Safety
  - Safe and well tolerated in patients with advanced AIDS

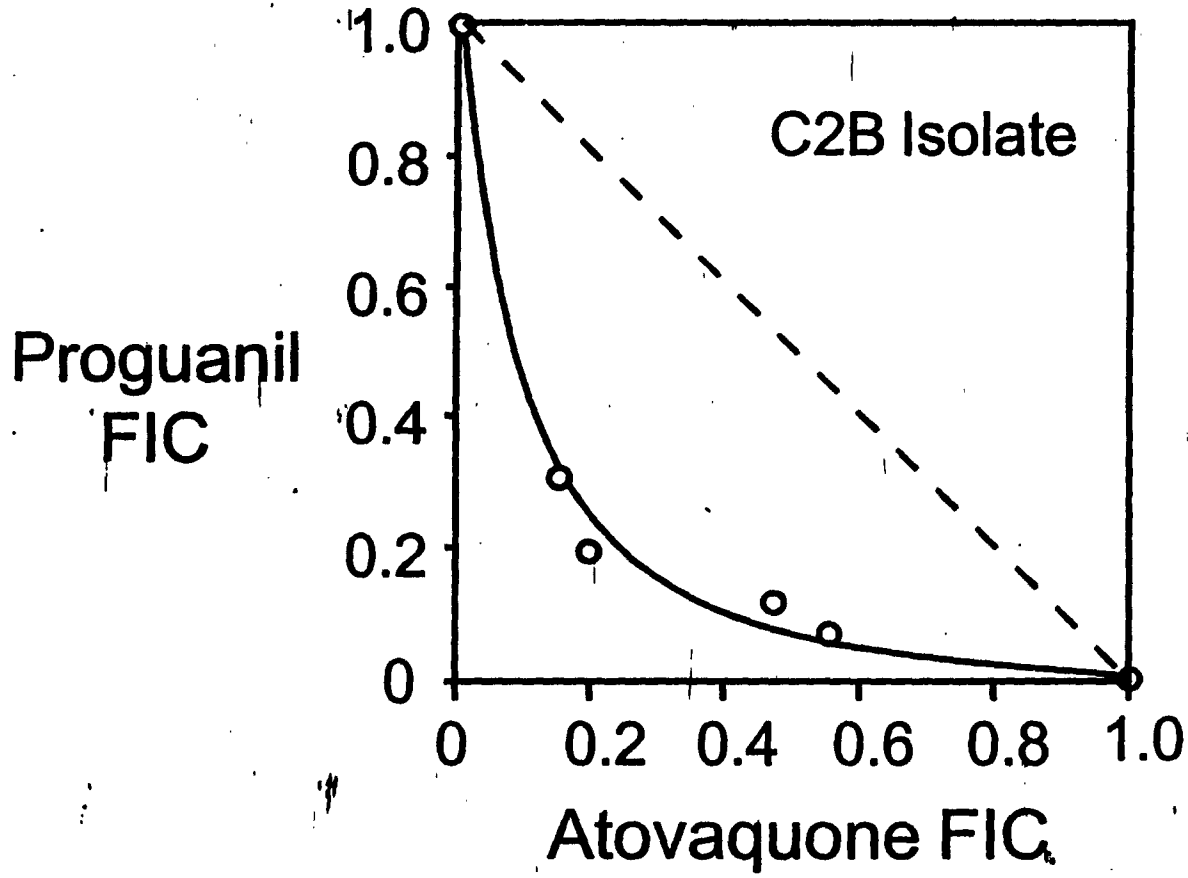
Antimalarial Activity of Proguanil

- Dihydrofolate reductase inhibitor
- *In vitro* IC_{50} (as cycloguanil) 15 - 79 nM
- Efficacy in mouse malaria model
- Active as causal prophylactic

Clinical Characteristics of Proguanil

- Efficacy
  - Effective for malaria prophylaxis (generally used with chloroquine)
- Safety
  - Long history of safe use

Atovaquone/Proguanil Synergy *in vitro*



Ref. Canfield *et al.* Exp. Parasitol. 80, 373-381 (1995)

Efficacy of Atovaquone and/or Proguanil for *P. falciparum* Malaria

	No. patients cured/treated	Fraction cured
Atovaquone alone	59/89	66%
Proguanil alone	1/17	6%
Atovaquone & proguanil*	514/521	99%

*1000 mg ATQ + 400 mg PGN daily x 3

Comparative Efficacy of Atovaquone & Proguanil for *P. falciparum* Malaria

- Efficacy significantly better than chloroquine, amodiaquine, and mefloquine in areas with drug-resistant malaria
- Efficacy similar to Fansidar, halofantrine, and quinine/tetracycline in areas with malaria sensitive to these drugs

Atovaquone/Proguanil Safety Profile

- Adverse events generally mild and of limited duration
- Abdominal pain, headache, anorexia, nausea, vomiting,, diarrhea and coughing were the most commonly reported adverse events
- Occasional elevation of liver enzymes

Efficacy of Atovaquone/Proguanil for Malaria Prophylaxis in Kenya

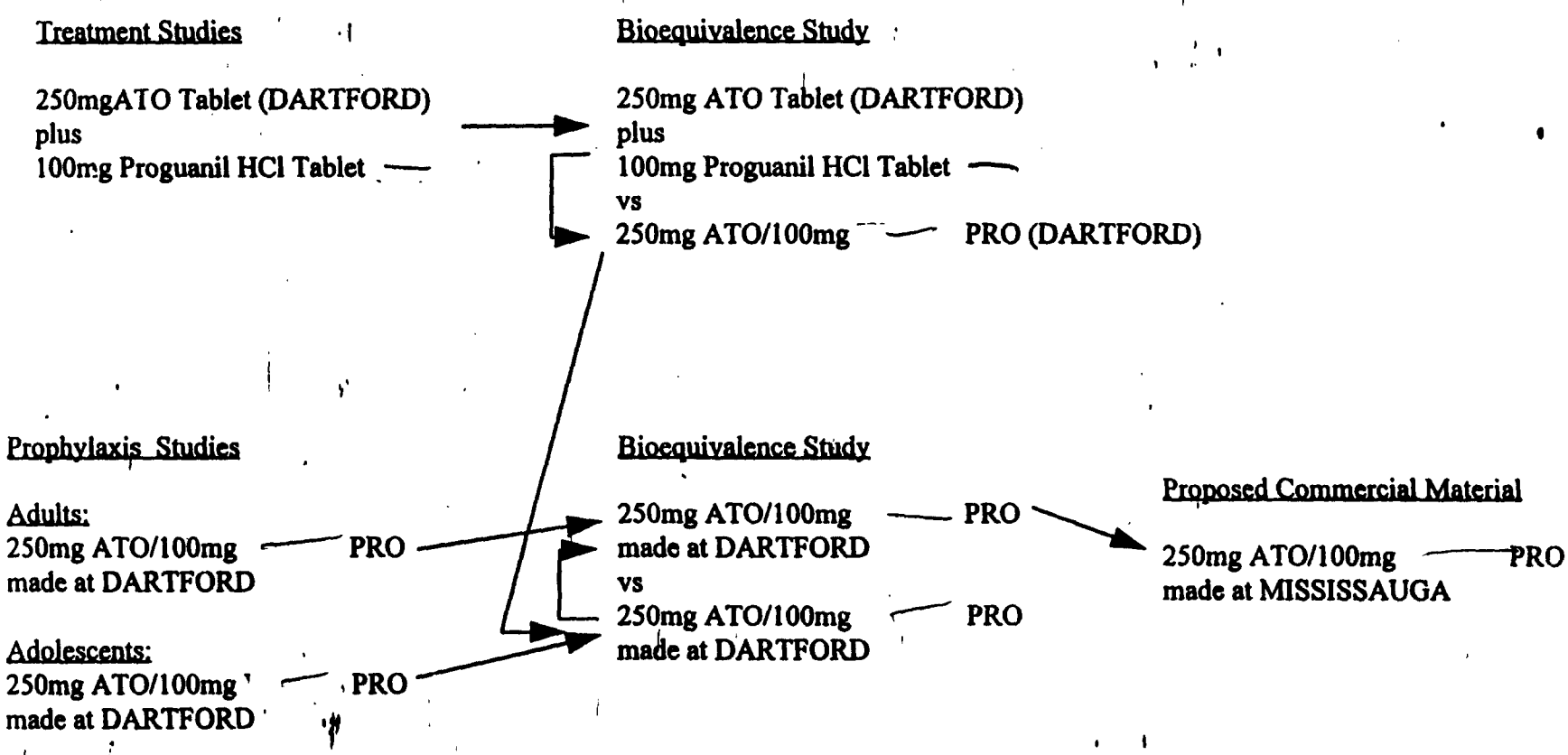
	No. of patients infected/enrolled	Efficacy
Placebo	28/56	
Malarone* 2 tablets/d	0/61	100%
Malarone* 1 tablet/d	0/60	100%

*250 mg ATQ + 100 mg PGN per tablet

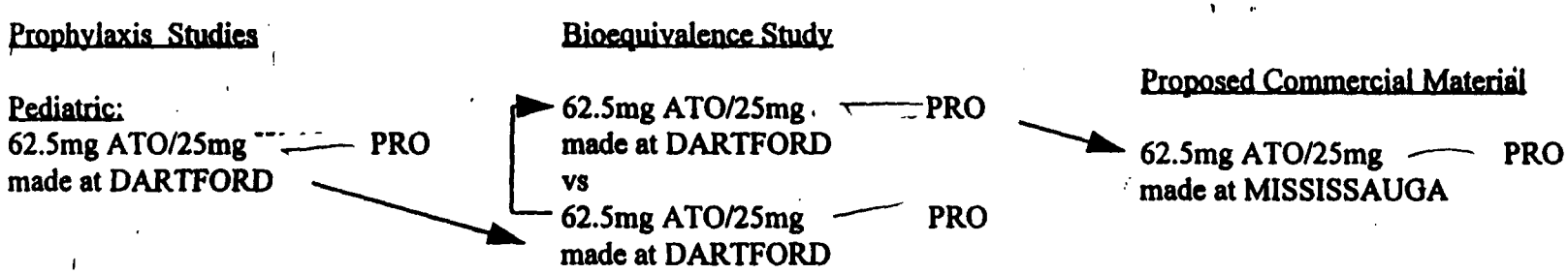
Summary Information on Malarone

- Fixed dose, synergistic combination of atovaquone and proguanil
- Highly effective treatment for drug-sensitive and drug-resistant falciparum malaria
- Favorable safety profile
- 100% efficacy in phase 2 prophylaxis trial

Malarone Tablet (Full Strength)
Bioequivalence Bridging and Clinical Studies



Malarone Tablet (Quarter Strength)
Bioequivalence Bridging and Clinical Studies



MEMORANDUM

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

Date: June 29, 1999

From: Robert Hopkins M.D., M.P.H. & T.M.
Medical Team Leader, DSPIDP

Through: Mark Goldberger, Division Director DSPIDP
Sandra Kweder, Acting Office Director ODE IV

To: NDA 21-078

Subject: Need for additional bioequivalence studies for Malarone

Background:
During the clinical pharmacology review of the Malarone NDA, it was found that Glaxo Wellcome did not perform bioequivalence studies that link the Malarone to-be-marketed products manufactured in Canada to those used in the clinical trials that were manufactured in the UK. This is true for both the quarter strength (QS) and full strength tablets (FS).

As outlined in the clinical pharmacology review, there is reason to be concerned regarding the potential for lack of bioequivalence between the to-be-marketed formulations and those formulations used in the clinical trials. Of particular concern is the lack of bioequivalence demonstrated in study MALB1004 comparing the AUC for atovaquone between the QS tablet with a — source proguanil versus the QS tablet with a — source progunil (Ratio = — 95% CI 0.71-0.88).

The final recommendation in the clinical pharmacology review stated that a bioequivalence study should be conducted to link the to-be-marketed formulations (FS and QS tablets using a — source proguanil) manufactured in Canada to the UK formulations (FS and QS tablets).

Under normal conditions we would expect that a link be demonstrated between the product used in clinical trials and the to-be marketed product. It is my opinion that lack of data showing bioequivalence should not preclude approval of the either the QS or the FS Malarone products. This is mainly based on a public health need for the QS and FS Malarone products in preventing and treating multi-drug resistant *P. falciparum* malaria that is not met with currently approved anti-malarials. The market for the QSformulation is likely to be less than that for the full strength formulation as its indication is limited to prophylaxis of *P. falciparum* malaria among pediatric populations. In contrast, the FS

formulation is to be indicated for the treatment and prophylaxis of *P. falciparum* in pediatric and adult populations. Given the public health concern regarding emerging multi-drug resistant *P. falciparum* malaria I recommend deferring or waiving the requirement to demonstrate bioequivalence of the atovaquone component of Malarone until after approval.

In conjunction with Glaxo Wellcome, we have developed the following plan to address this issue. Glaxo Wellcome has agreed to perform two additional phase 4 clinical studies: one in an adult population with the to-be-marketed full strength product and one in a pediatric population with the quarter strength product manufactured in Canada. The adult study is to be a randomized, open-label, uncontrolled study to evaluate the safety and efficacy of Malarone for treatment of adults with acute *P. falciparum* malaria in Thailand using tablets manufactured in Canada. The pediatric study is to be a randomized, double-blind, placebo-controlled, parallel group study to evaluate the suppressive prophylactic activity of Malarone in children at risk of developing *P. falciparum* malaria. It is my recommendation to defer the need to conduct additional bioequivalence studies until the results of the two above mentioned phase 4 studies are completed. Following FDA review of the results of these two studies, a decision should be made regarding the need to conduct additional bioequivalence studies. If these studies are deemed necessary, the bioequivalence studies should be designed to demonstrate bioequivalence for the atovaquone component of marketed full strength and quarter strength tablets and the full strength tablet used in the clinical studies supporting approval.

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NDA 21-078

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