CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-078

APPROVAL LETTER

HFD-540/V. JUE...

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-078

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

JUL 14 2000

Glaxo Wellcome Inc.
Attention: Thomas Shumaker
Project Director, Regulatory Affairs
Five Moore Drive
PO Box 13398
Research Triangle Park, NC 27709

Dear Mr. Shumaker:

Please refer to your new drug application (NDA) dated December 29, 1998, received December 30, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MALARONE™ (atovaquone and proguanil hydrochloride) Tablets. This application provides for MALARONE Tablets containing 250 mg atovaquone and 100 mg proguanil hydrochloride and MALARONE Pediatric Tablets containing 62.5 mg atovaquone and 25 mg proguanil hydrochloride.

We acknowledge receipt of your submissions dated as follows:

July 8, 1999	December 23, 1999	February 11, 2000
July 22, 1999	January 12, 2000	March 21, 2000
July 29, 1999	January 17, 2000	April 19, 2000
August 10, 1999	January 19, 2000 (2)	July 12, 2000 (2)
December 21, 1999		

We also refer to our approvable letter dated June 30, 1999 and to your resubmission dated January 19, 2000 and received on January 21, 2000. The January 19, 2000 resubmission constituted a complete response to our June 30, 1999 action letter. The user fee due date for this application is July 21, 2000.

This new drug application provides for the use of MALARONE (atovaquone and proguanil hydrochloride) Tablets for the treatment and prevention of *Plasmodium falciparum* malaria.

We have completed the review of this application, including your resubmission, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted labeling (text for the package insert submitted July 12, 2000 and immediate container labels submitted July 29, 1999). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

As you are aware from our recent discussions, we are committed to working with you to minimize the potential for medication errors related to confusion that might occur between the two strengths of MALARONE tablets. To address this, we refer to your submission dated July 12, 2000. The July 12, 2000 submission outlines the agreement you have made with the Agency to begin discussions involving modifications to the immediate container labels for MALARONE Tablets and MALARONE Pediatric Tablets by October 13, 2000. This submission also outlines the agreement you have made to begin discussions with the Agency by October 13, 2000 regarding the development of specific measures to allow healthcare providers and patients to clearly distinguish between MALARONE Tablets and MALARONE Pediatric Tablets.

Please submit 20 copies of the FPL as soon as they are available, in no case more than 30 days after they are printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-078." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments with agreed upon completion dates specified in your submission dated June 8, 2000. These commitments, which supersede the Phase 4 commitments and completion dates from your submission dated June 29, 1999, are listed below.

Glaxo Wellcome Inc. will:

1. Conduct an international, randomized, double-blind study to compare the safety and efficacy of MALARONE versus mefloquine for chemoprophylaxis against malaria in non-immune travelers. The final study report will be submitted before February 2001.

2. Conduct an international, randomized, double-blind study to compare the safety and efficacy of MALARONE versus chloroquine/proguanil hydrochloride for chemoprophylaxis against malaria in non-immune travelers. The final study report will be submitted before February 2001.

3. Conduct an international, randomized, open-label study to compare the safety and efficacy of MALARONE versus chloroquine/proguanil hydrochloride for chemoprophylaxis against malaria in non-immune pediatric travelers. The final study report will be submitted before February 2001.

4. Conduct a randomized, double-blind, placebo-controlled study of MALARONE as a causal prophylactic agent against mosquito-transmitted *P. falciparum* malaria in healthy non-immune volunteers. The final study report will be submitted before February 2001.

5. Conduct an uncontrolled study to evaluate the safety and efficacy of MALARONE for treatment of adults with acute *Plasmodium falciparum* malaria in Thailand using 250 mg atovaquone/100 mg proguanil tablets manufactured in Canada. The final study report will be submitted before April 2001.

   Note: If the lower bound of the two-sided 95% confidence interval for efficacy is 90% or greater, in the per protocol population, then a bioequivalence study will not be needed. If the lower bound of the two-sided 95% confidence interval for efficacy is less than 90%, in the per protocol population, then the need for a bioequivalence study to link the to-be-marketed product (FS-J) manufactured in Canada to the UK product (FS) will be evaluated in the context of all of the efficacy data provided.

6. Conduct a randomized, double-blind, placebo-controlled, parallel group study to evaluate the suppressive prophylactic activity of MALARONE in pediatric patients at risk of developing *P. falciparum* malaria using 62.5 mg atovaquone/25 mg proguanil tablets manufactured in Canada. The final study report will be submitted before April 2001.

   Note: If the lower bound of the two-sided 95% confidence interval for protective efficacy is 60% or greater, in the per protocol population, then a bioequivalence study will not be needed. If the lower bound of the two-sided 95% confidence interval for protective efficacy is less than 60%, in the per protocol population, then the need for a bioequivalence study to link the to-be-marketed product (QS-J) manufactured in Canada to the UK product (QS) will be evaluated in the context of all of the efficacy data provided.

7. Conduct an open-label, parallel group, single oral dose study to investigate the pharmacokinetics of MALARONE in subjects with severe renal impairment compared to healthy subjects. The final study report will be submitted before February 2001.

8. Conduct an open-label, parallel group, single oral dose study to investigate the pharmacokinetics of MALARONE in subjects with mild to moderate hepatic impairment compared to healthy subjects. The final study report will be submitted before February 2001.

9. Collaborate with the CDC to prepare and submit an annual report of all notified malaria cases in the United States. The report will include both information on the prophylaxis used in each case and utilization data for all U.S. approved anti-malarial prophylactic drugs calculated from available prescription data. This will be used to evaluate malaria breakthrough rates for MALARONE compared with other prophylactic modalities. Modeled on the concept protocol for the study sent to the Division of Special Pathogen and Immunologic Drug Products on July 1, 1999, this report will be prepared for the first five years following approval of the NDA, at which time the usefulness of continuing this reporting mechanism will be discussed.

10. Conduct the following FIVE non-clinical pharmacology and toxicology studies:

    a) Segment I (Fertility) reproductive toxicology study with proguanil in rats,
    b) Segment III (Pre- and post-natal development) reproductive toxicology study with proguanil in rats,
    c) Ninety day pre-oncogenicity study with proguanil in mice,
    d) Carcinogenicity study with proguanil in mice,
    e) Carcinogenicity study with proguanil in rats.

    Reports of Segment I (fertility) and Segment III (pre- and post-natal development) studies with proguanil in rats will be submitted by August 2000. Reports of completed carcinogenicity studies with proguanil in mice and rats will be submitted by the second quarter of 2003. The protocols for the carcinogenicity studies with proguanil in mice and rats should be submitted for review by the executive CAC prior to beginning the studies.

11. Develop a dissolution method that avoids using [redacted] or other extreme conditions as the dissolution medium for the atovaquone component of MALARONE. This method will be developed and reported to the Agency before July 13, 2001.

Protocols, data, and final reports for these eleven items should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA identified as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

In addition to the above Phase 4 commitments, we note that Glaxo Wellcome has agreed to work with the Agency to establish a regulatory specification for [redacted] in the proguanil hydrochloride drug substance if the levels of [redacted] in the [redacted] proguanil hydrochloride exceed [redacted]. We request that Glaxo Wellcome notify the Agency within sixty days of becoming aware of this finding.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have fulfilled the pediatric study requirements at this time for pediatric patients weighing greater than or equal to eleven kilograms. We are deferring submission of your final pediatric study reports for pediatric patients weighing less than eleven kilograms and greater than or equal to five kilograms until April 1, 2002. We are waiving the pediatric study requirement for pediatric patients weighing less than five kilograms for this action on this application.

We received your Proposed Pediatric Study Request dated June 8, 2000. As we discussed during our May 22, 2000 teleconference, we will issue a Written Request for MALARONE addressing the pediatric studies for the indications outlined in this approval letter.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Valerie Jensen, R.Ph., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

/S/

Sandra L. Kweder, M.D.
Acting Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Archival NDA 21-078
HFD-590/Div. Files
HFD-590/V.Jensen
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-104/ADRA (with labeling)
HFD-102/Post-Marketing PM
HFD-104/Peds/V.Kao (with labeling)
HFD-104/Peds/T.Crescenzi (with labeling)
HFD-40/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-095/DDMS-IMT (with labeling)
HFD-830/DNDC Division Director
DISTRICT OFFICE

Concurrence:
HFD-590/Acting Dir./R. Albrecht
HFD-590/TL/R. Roca
HFD-590/MO/A. Meyerhoff
HFD-590/MO/L. Sacks
HFD-880/Biopharm TL/ F. Ajayi
HFD-880/Dir DPE III/J. Lazor
HFD-725/Stat TL/ K. Higgins
HFD-725/Dir DOB III/ M. Huque
HFD-590/CPMS/E. Frank
HFD-590/Pharm/tox TL/K. Hastings
HFD-530/Assoc. Dir/Pharm/tox/J. Farrelly
HFD-590/Micro. Acting/S. Bala
HFD-590/Chem TL/N. Schmuff
HFD-880/Dir DNDC III/C. Chen
HFD-104/PDIT/MO/R. Roberts
HFD-104/PDIT/PM/T. Crescenzi

Drafted by: vj
Initialed by:
final:
filename: approvalmal

APPROVAL (AP) (with Phase 4 Commitments)

To Post-Marketing PM:
Phase IV commitments #5, #6, and #9 will be considered fulfilled when the reports are submitted. Separate phase IV commitments will be made if necessary due to results.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-078

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

JUN 30 1999

Glaxo Wellcome, Inc.
Attention: Thomas Shumaker
Project Director, Regulatory Affairs
Five Moore Drive
PO Box 13398
Research Triangle Park, NC 27709

Dear Mr. Shumaker:

Please refer to your new drug application (NDA) dated December 29, 1998, received December 30, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MALARONE (250mg atovaquone/100mg proguanil and 62.5mg atovaquone/ 25mg proguanil) Tablets.

We acknowledge receipt of your submissions dated as follows:

January 8, 1999	April 23, 1999	June 3, 1999
January 27, 1999	April 27, 1999	June 4, 1999
February 4, 1999	April 29, 1999	June 14, 1999 (2)
February 24, 1999	May 3, 1999	June 16, 1999
March 3, 1999	May 14, 1999	June 17, 1999 (2)
March 16, 1999	May 17, 1999 (2)	June 18, 1999
March 31, 1999 (3)	May 21, 1999	June 21, 1999
April 16, 1999 (2)	May 24, 1999	June 29, 1999 (2)
April 21, 1999 (2)	May 26, 1999	

The User Fee goal date for this application is June 30, 1999.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the inspector. Satisfactory inspections will be required before this application may be approved.

In addition, it will be necessary for you to submit final printed labeling (FPL) for the drug. The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted June 29, 1999, immediate container and carton labels submitted June 14, 1999).

Please submit 20 copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Special Pathogen and Immunologic Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

We remind you of your Phase 4 commitments specified in your submission dated June 29, 1999. These commitments, along with any completion dates agreed upon, are listed below.

PHASE 4 AGREEMENTS

1. Conduct an international, randomized, double-blind study to compare the safety and efficacy of MALARONE versus mefloquine for chemoprophylaxis against malaria in non-immune travelers. The final study report will be submitted before February 2001.

2. Conduct an international, randomized, double-blind study to compare the safety and efficacy of MALARONE versus chloroquine/proguanil hydrochloride for chemoprophylaxis against malaria in non-immune travelers. The final study report will be submitted before February 2001.

3. Conduct an international, randomized, open-label study to compare the safety and efficacy of MALARONE versus chloroquine/proguanil hydrochloride for chemoprophylaxis against malaria in non-immune pediatric travelers. The final study report will be submitted before February 2001.

4. Conduct a randomized, double-blind, placebo-controlled study of MALARONE as a causal prophylactic agent against mosquito-transmitted *P. falciparum* malaria in healthy non-immune volunteers. The final study report will be submitted before February 2001.

5. Conduct a randomized open-label, uncontrolled study to evaluate the safety and efficacy of MALARONE for treatment of adults with acute *Plasmodium falciparum* malaria in Thailand using 250mg atovaquone/100mg proguanil tablets manufactured in Canada. The final study report will be submitted before April 2001.

   If the lower bound of the two-sided 95% confidence interval for efficacy is 90% or greater, in the per protocol population, then a bioequivalence study will not be needed. If the lower bound of the two-sided 95% confidence interval for efficacy is less than 90%, in the per protocol population, then the need for a bioequivalence study to link the to-be-marketed formulation (FS-J) manufactured in Canada to the UK formulation (FS) will be evaluated in the context of all of the efficacy data provided.

6. Conduct a randomized, double-blind, placebo-controlled, parallel group study to evaluate the suppressive prophylactic activity of MALARONE in pediatric patients at risk of developing *P. falciparum* malaria using 62.5mg atovaquone/25mg proguanil tablets manufactured in Canada. The final study report will be submitted before April 2001.

   If the lower bound of the two-sided 95% confidence interval for protective efficacy is 60% or greater, in the per protocol population, then a bioequivalence study will not be needed. If the lower bound of the two-sided 95% confidence interval for protective efficacy is less than 60%, in the per protocol population, then the need for a bioequivalence study to link the to-be-marketed formulation (QS-J) manufactured in Canada to the UK formulation (QS) will be evaluated in the context of all of the efficacy data provided.

7. Conduct an open-label, parallel group, single oral dose study to investigate the pharmacokinetics of MALARONE in subjects with severe renal impairment compared to healthy subjects. The final study report will be submitted before February 2001.

8. Conduct an open-label, parallel group, single oral dose study to investigate the pharmacokinetics of MALARONE in subjects with mild to moderate hepatic impairment compared to healthy subjects. The final study report will be submitted before February 2001.

9. Collaborate with the CDC to prepare and submit an annual incidence report of malaria as an adjunct to the NDA Annual Report for MALARONE Tablets. This report will include data on reported cases of malaria in the United States, as reported to the CDC, and incidence data for all US approved anti-malarial drugs, as calculated from available prescription data and will be modeled on the concept protocol for the study, sent to the Division on June 1, 1999. This report will be prepared for the first 5 years following approval of the NDA, at which time the usefulness of continuing this reporting mechanism will be discussed.

10. Conduct the following SIX non-clinical pharmacology and toxicology studies:

    a) Segment I (Fertility) reproductive toxicology study with proguanil in rats,
    b) Segment III (Pre- and post-natal development) reproductive toxicology study with proguanil in rats,
    c) 90-day pre-oncogenicity study with proguanil in mice,
    d) Carcinogenicity study with proguanil in mice,
    e) Carcinogenicity study with proguanil in rats.
    f) A battery of genotoxicity assays to determine the potential hazard of the proguanil contaminant 1-(4-chlorophenyl) urea.

    Reports of Segment I (fertility) and Segment III (pre- and post-natal development) studies with proguanil in rats will be submitted by August and December, 1999, respectively. Reports of completed carcinogenicity studies with proguanil in mice and rats will be submitted by the third quarter of 2002.

11. Develop a dissolution method that avoids using [redacted] or other extreme conditions as the dissolution medium for the atovaquone component for MALARONE. This method will be developed and reported to the Agency within one year of the approval date of the NDA.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

If you have any questions, contact Mary Dempsey, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

/S/

Sandra L. Kweder, M.D.
Acting Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Archival NDA 21-078
HFD-590/Div. Files
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HFD-95/DDMS (with labeling)
HFD-830/DNDC Division Director
DISTRICT OFFICE
HFD-590/Chem/J Smith
HFD-880/Biopharm/H Mahayni
HFD-725/Stat/J Jiang
HFD-590/Pharm/Tox/S Kunder
HFD-590/ChemTL/N Schmuff
HFD-590/MO/A Meyerhoff
HFD-590/MO/L Sacks
HFD-590/Micro/S Bala

Concurrence:
HFD-590/Dir/M Goldberger
HFD-590/DepDir/R Albrecht electronic 30-99
HFD-590/MTL/R Hopkins
HFD-590/ActChemTL/M Seggel electronic 6-29-99
HFD-830/Dir DNDC III/C Chen electronic 6-30-99
HFD-880/Biopharm TL/F Ajayi electronic 6-29-99
HFD-880/Dir DPE III/ J Lazor electronic 6-29-99
HFD-725/StatTL/N Silliman
HFD-725/Dir DOB III/M Huque 6/30/99
HFD- 590/CPMS/E Frank
HFD-590/Pharm/ToxTL/K Hasting
[redacted]Dir/Pharm/Tox/J Farrelly electronic 6-29-99
HFD-590/Micro ActTL/L Gosey electronic 6-29-99

Drafted by: mjd/June 30, 1999
Initialed by:
final:
filename: v:dspidp\dempsey\21-078\MALARONE approvable

APPROVABLE (AE) (~~with~~ Phase 4 commitments)