GlaxoWellcome

ORIGINAL

May 24, 1999

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

ORIG AMENDMENT

Re: NDA 21-078; MALARONE™ (atovaquone and proguanil hydrochloride) Tablets for the Treatment and Prevention of Malaria
Request for Review of Labeling and Nomenclature Committee Decision

Dear Dr. Goldberger:

Reference is made to the facsimile received from your Division on April 12, 1999, outlining the reason that the CDER Labeling and Nomenclature Committee had not approved of the name MALARONE for our brand of atovaquone and proguanil hydrochloride tablets. Reference is also made to our submission of a response and request for re-consideration of that decision on April 21, 1999.

We are herewith asking that the Division review the recommendation of the CDER Labeling and Nomenclature Committee (Attachment 1) and our response (Attachment 2). We believe that use of the name MALARONE Tablets for this medicine does not create any substantial risk of confusion or error, and we respectfully ask that the Division review the information provided and allow our use of the proprietary name "MALARONE Tablets" for this combination drug product of atovaquone and proguanil hydrochloride.

This submission is made in duplicate to the NDA file. An additional four desk copies are being sent directly to Ms. Dempsey. If you have any questions regarding this correspondence, please contact me at 919-483-9324.

Sincerely,

Thomas K. Shumaker
Project Director
Regulatory Affairs

Glaxo Wellcome Research and Development

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

Telephone
919 248 2100

A Division of
Glaxo Wellcome Inc.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEFACSIMILE

DATE: May 11, 1999

TO: Tom Shumaker, Regulatory Affairs

FROM: Mary Dempsey, Regulatory Project Manager 5/11/99

THROUGH: Mark J. Goldberger, M.D., M.P.H., Division Director
Robert Hopkins, M.D., M.P.H., T.M., Medical Team Leader
John Lazor, Ph.D., Director DPE III
Norman Schmuff, Ph.D., Chemistry Team Leader
Arzu Selen, Ph.D., Deputy Director DPE III
Andrea Meyerhoff, M.D., M.Sc., DTMH, Medical Officer
Funmilayo Ajayi, Ph. D., Team Leader, DPE III,
Office of Clinical Pharmacology and Biopharmaceutics

APPLICANT: Glaxo Wellcome

NDA: 21-078

DRUG: Malarone (atovaquone and proguanil)

SUBJECT: Preparation for telecon

In preparation for our teleconference scheduled for May 12, 1999, please consider the following questions:

1. Please provide an explanation of what happened to the manufacturing process, after changing the source of proguanil, that resulted in failure to demonstrate BE of atovaquone when Malarone tablets (containing proguanil from was compared to Malarone tablets (containing proguanil from

2. Given the issue with BE noted above, how do you propose to demonstrate that the products manufactured in Canada are bioequivalent to those products manufactured in UK?

3. What is the justification for the use of the proposed dissolution method and specification? Please include the dissolution method development and history for Malarone, including your experience with other dissolution methods.

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Division of Special Pathogens and Immunologic Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: May 11, 1999 Number of Pages (including cover sheet): 2
TO: Tom Shumaker
COMPANY: Glaxo
FAX NUMBER: 919-483-5756
MESSAGE: RE: Preparation for Telecon

NOTE: We are providing the attached information via telefacsimile 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.

FROM: Mary Dempsey
TITLE: Project Manager

TELEPHONE: (301) 827-2127 FAX NUMBER:(301) 827-2475

CC: Division file
NDA 21-078
5901 (S)
5901 (S)
5901 (S)
5901 (S)
8801 (S)
8801 (S)

5901/Biopharm, (S)
5901/P.M., (S)

********** -COMM. JOURNAL- ********** DATE MAY-11-1999 ***** TIME 14:05 *** P.01

MODE = MEMORY TRANSMISSION START=MAY-11 14:03 END=MAY-11 14:05

FILE NO.= 186

STN NO.	COM	ABBR NO.	STATION NAME/TEL.NO.	PAGES	DURATION
001	OK	8	919194835756	002/002	00:00'43"

-FOOD & DRUG ADMIN.

********** - ***** - 301 827 2474- *********

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Special Pathogens and Immunologic Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: May 11, 1999
TO: Tom Shumaker
COMPANY: Glaxo
FAX NUMBER: 919-483-5756
MESSAGE: RE: Preparation for Telecon

Number of Pages (including cover sheet): 2

NOTE: We are providing the attached information via telefacsimile 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.

FROM: Mary Dempsey
TITLE: Project Manager

TELEPHONE: (301) 827-2127 FAX NUMBER:(301) 827-2475

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEFACSIMILE

DATE: May 7, 1999

TO: Tom Shumaker, Regulatory Affairs

FROM: Mary Dempsey, Regulatory Project Manager

THROUGH: Robert Hopkins, M.D., M.P.H., T.M., Medical Team Leader RWH
Norman Schmuff, Ph.D., Chemistry Team Leader
John Smith, Ph.D., Chemist
Funmilayo Ajayi, Ph. D., Team Leader, DPE III,
Office of Clinical Pharmacology and Biopharmaceutics
Houda Mahayni, RPh., Ph.D., Clin. Pharm. & Biopharmaceutics
Reviewing Officer

APPLICANT: Glaxo Wellcome

NDA: 21-078

DRUG: Malarone (atovaquone and proguanil)

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

SUBJECT: Information request

Please let us know whether you have any multi-point comparative dissolution data comparing any of the full-strength batches made in Canada with any of the full-strength batches made in UK and/or used in the clinical trials.

Please provide this information as soon as possible.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Special Pathogens and Immunologic Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: May 7, 1999 Number of Pages (including cover sheet): 2
TO: Tom Shumaker
COMPANY: Glaxo
FAX NUMBER: 919-483-5756
MESSAGE: RE: Information Request

NOTE: We are providing the attached information via telefacsimile 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.

FROM: Mary Dempsey
TITLE: Project Manager

TELEPHONE: (301) 827-2127 FAX NUMBER:(301) 827-2475

MODE = MEMORY TRANSMISSION START=MAY-07 15:30 END=MAY-07 15:31

FILE-NO.= 164

STN NO.	COM	ABBR NO.	STATION NAME/TEL.NO.	PAGES	DURATION
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-FOOD & DRUG ADMIN. -

********** - - ***** - 301 827 2474- *********

DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Division of Special Pathogens and Immunologic Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: May 7, 1999 Number of Pages (including cover sheet): 2
TO: Tom Shumaker
COMPANY: Glaxo
FAX NUMBER: 919-483-5756
MESSAGE: RE: Information Request

NOTE: We are providing the attached information via telefacsimile 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.

FROM: Mary Dempsey
TITLE: Project Manager

TELEPHONE: (301) 827-2127 FAX NUMBER:(301) 827-2475

U.S. Regulatory Affairs - Glaxo Wellcome Inc.

Facsimile Transmission

TO: Ms. Mary Dempsey DATE: April 29, 1999
COMPANY: DSPIDP, CDER, FDA FAX NO.: 9-1-301-827-2520
TOTAL NO. OF PAGES: 7 PHONE NO.:

MESSAGE: NDA 21-078
MALB2002 Questions

Ms. Dempsey,

Attached is our response to the April 27, 1999 facsimile from Dr. Sacks regarding malaria blood test results for atovaquone treated patients in MALB2002. We will also submit this information in hard copy, along with the diskette, today.

Please contact me at 919-483-9324 regarding this information and for any additional questions concerning Malarone.

Thank you very much,

Tom Shumaker

FROM:
Thomas Shumaker
US Regulatory Affairs
Glaxo Wellcome Inc.
5 Moore Drive
Research Triangle Park
North Carolina 27709

Phone: (919) 483-9324
Fax: (919) 483-5756

DISTRIBUTE COPIES TO:
Dr. Sacks

GlaxoWellcome

April 29, 1999

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 21-078; MALARONE™ (atovaquone and proguanil hydrochloride) Tablets for the Treatment and Prevention of Malaria
Response to FDA Request/Comment: Clinical, MALB2002

Dear Dr. Goldberger:

Reference is made to the request received by facsimile on April 27, 1999 from the Medical Reviewer of the Malarone NDA in regards to Study MALB2002. Reference is also made to our submission on February 24, 1999, of a diskette with SAS datasets of safety and efficacy parameters for Study MALB2002. Below please find our response to the April 27, 1999, request. The request is first repeated in bold, followed by our response.

Please provide all malaria blood test results (QBC/PCR/Culture/smear) performed on the 12 atovaquone treated subjects from day 21 till end of study.

Response: Section 4.1.3. of the protocol for Study MALB2002 is in error regarding the testing to be done during follow-up. Testing during follow-up was done according to Appendix IX; *Study Flowsheet* of protocol MALB2002 (Volume 57, NDA page 202 of the NDA). Beyond Study Day 21 blood was collected for QBC and smears, but not for culture or PCR. The attached listing shows the QBC real time, QBC per Johns Hopkins Hospital lab, and the thick smear Johns Hopkins Hospital lab results for the 12 atovaquone-treated patients from Day 21 until the end of the study at Week 12. The QBC and smear data are also contained, in a slightly different format, in the diskette with SAS datasets of safety and efficacy parameters for Study MALB2002, submitted on February 24, 1999. An additional copy of that diskette is included with one of the desk copies of this 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.

This submission is made in duplicate to the NDA file. In addition, three desk copies, including an additional copy of the Study MALB2002 diskette, are being sent directly to Ms. Mary Dempsey of your Division. If you have any questions regarding this correspondence, please contact me at 919-483-9324.

Sincerely,

Thomas K. Shumaker

Thomas K. Shumaker
Project Director
Regulatory Affairs

WITHHOLD 4 PAGE (S)

U.S. Regulatory Affairs - Glaxo Wellcome Inc.
Facsimile Transmission

TO: Ms. Mary Dempsey DATE: April 28, 1999
COMPANY: DSPIDP, CDER, FDA FAX NO.: 9-1-301-827-2520
TOTAL NO. OF PAGES: 2 PHONE NO.:

MESSAGE: NDA 21-078
Microbiology and MALB2002 Questions

Ms. Dempsey,

Attached is our response to the April 23, 1999, request from the Microbiology reviewer regarding proguanil and causal prophylaxis. Literature references to support this response have been ordered, but will take a few more days to arrive. The response will be submitted in hard copy, along with the references, when they arrive.

The response to the April 27, 1999 facsimile from Dr. Sacks should be available on Thursday, the 29th. We will submit it by facsimile and hard copy.

Please contact me at 919-483-9324 regarding this information and for any additional questions concerning Malarone.

Thank you very much,

Tom Shumaker

Tom Shumaker

FROM:
Thomas Shumaker
US Regulatory Affairs
Glaxo Wellcome Inc.
5 Moore Drive
Research Triangle Park
North Carolina 27709

Phone: (919) 483-9324
Fax: (919) 483-5756

DISTRIBUTE COPIES TO: Dr. Bala
Dr. Sacks

MALARONE Tablets NDA 21-078

Reference is made to the requests received on April 23, 1999 from the Microbiology Reviewer of the Malarone NDA. Below please find our response to these requests. The request is first repeated in bold, followed by our response.

Are the statements regarding proguanil on pages 13 and 14 of Volume 34, "Proguanil is a true causal prophylactic, etc", based on the study by Erickson?

Response: The statement that proguanil is a true causal prophylactic is based on animal studies with rodent parasites (1) and clinical studies in human volunteers challenged by the bites of malaria-infected mosquitoes (2,3).

Have there been any animal studies where the animals were pretreated with atovaquone and proguanil and then infected with malarial sporozoites?

Response: Animal studies have been performed where the animals were treated with atovaquone (4) or proguanil (2) shortly before or after being infected with malarial sporozoites. These studies demonstrated that both atovaquone and proguanil have causal prophylactic activity in animal models of sporozoite-induced malaria.

The specific supporting references are identified below. They have been ordered from outside sources and will be supplied as soon as they are received.

1. Peters W, Davies EE, Robinson BL. The chemotherapy of rodent malaria, XXIII. Causal prophylaxis, part II: Practical experience with *Plasmodium yoelii nigeriensis* in drug screening. Ann Trop Med Parasitol 1975; 69:311-328.
2. Fairley NH. Researches on paludrine (M.4888) in malaria. An experimental investigation undertaken by the L.H.Q. Medical Research Unit (A.I.F.), Cairns, Australia. Trans R Soc Trop Med 1946; 40:105-151.
3. Covell G, Nicol WD, Shute PG, Maryon M. "Paludrine" (proguanil) in prophylaxis and treatment of malarial infections caused by a West African strain of *P falciparum*. BMJ 1949; 1:88-91.
4. Davies CS, Pudney M, Matthews PJ, Sinden RE. The causal prophylactic activity of the novel hydroxynaphthoquinone 566C80 against *Plasmodium berghei* infections in rats. Acta Leidensia 1989; 58:115-128.

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEFACSIMILE

DATE: April 27, 1999

TO: Tom Shumaker, Regulatory Affairs
Glaxo Wellcome

FROM: Mary Dempsey, Regulatory Project Manger

THROUGH: Leonard Sacks, M.D., Medical Officer

NDA: 21-078

DRUG: Malarone (atovaquone and proguanil)

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

Related Document: N-000
Original NDA submission

SUBJECT: Request for Information

The Medical Officer has the following request for information:

According to protocol malB 2002, p 17 paragraph 4.1.3, outpatient follow-up continued till three months after challenge and blood tests for malaria were scheduled on alternate days from 23-33 and weekly till week 12.

Figure 1 indicates that no sample was available beyond day 21 in 14 of the 16 subjects. Listings for other blood tests (e.g. appendix B5) show follow-up beyond day 21 only for three atovaquone treated subjects (in each case, a single week 12 CBC).

Please provide all malaria blood test results (QBC/PCR/Culture/smear) performed on the 12 atovaquone treated subjects from day 21 till end of study.

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.

151

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

MODE = MEMORY TRANSMISSION START=APR-27 13:46 END=APR-27 13:47

FILE NO.= 037

STN NO.	COM	ABBR NO.	STATION NAME/TEL.NO.	PAGES	DURATION
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-FOOD & DRUG ADMIN.

********** - ***** - 301 827 2474- *********

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEFACSIMILE

DATE: April 27, 1999

TO: Tom Shumaker, Regulatory Affairs
Glaxo Wellcome

FROM: Mary Dempsey, Regulatory Project Manger

THROUGH: Leonard Sacks, M.D., Medical Officer

NDA: 21-078

DRUG: Malarone (atovaquone and proguanil)

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

Related Document: N-000
Original NDA submission

SUBJECT: Request for Information

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Figure 1 indicates that no sample was available beyond day 21 in 14 of the 16 subjects. Listings for other blood tests (e.g. appendix B5) show follow-up beyond day 21 only for three atovaquone treated subjects (in each case, a single week 12 CBC).

Please provide all malaria blood test results (QBC/PCR/Culture/smear) performed on the 12 atovaquone treated subjects from day 21 till end of study.

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

U.S. Regulatory Affairs - Glaxo Wellcome Inc.

Facsimile Transmission

TO: Ms. Mary Dempsey DATE: April 19, 1999
COMPANY: DSPIDP, CDER, FDA FAX NO.: 9-1-301-827-2520
TOTAL NO. OF PAGES: 3 PHONE NO.:

MESSAGE: NDA 21-078
Use of Response Factors in the NDA

Ms. Dempsey,

Attached is our response to the April 15, 1999, request of Dr. John Smith regarding the use of response factors for impurities in the CMC section of the Malarone NDA.

A hard copy of this information will be submitted to the NDA file.

Please contact me at 919-483-9324 regarding this information and for any additional questions concerning Malarone.

Thank you very much,

Tom

Tom Shumaker

FROM:
Thomas Shumaker
US Regulatory Affairs
Glaxo Wellcome Inc.
5 Moore Drive
Research Triangle Park
North Carolina 27709

Phone: (919) 483-9324
Fax: (919) 483-5756

DISTRIBUTE COPIES TO: Dr. John Smith

MALARONE Tablets NDA 21-078

Use of Response Factors for DS and DP Impurities

We apply response factors (if necessary) only to determination of impurities named and limited in specifications. Full details are as follows:

DRUG SUBSTANCES

1) Proguanil Hydrochloride

Response factors have been determined for the impurities named in the DS specification in Section D2.1 (Vol. 2, page 33) -

The method given in Section D4.5.11.3 (Vol. 2, page 53) prescribes the use of in the determination.

The method validation in Section D7.1.6 (Vol. 2, page 72) covers the determination of , for as respectively (wrt to proguanil HCl), and explains that only outside the range are applied in practice. This means that in the operation of the method in D4.5.11.3, a of is applied for , but that the for is taken as

2) Atovaquone (566C80)

We cross-referenced all information on atovaquone DS (see Vol. 2, page 7) to the MEPRON (atovaquone) Tablets NDA 20-259. The required information is in Vol. 2.3 of NDA 20-259.

The atovaquone DS specification is (see Vol. 2.3, page 422/423), and names and limits the impurities.

The method used (, see Vol. 2.3, page 431) specifies determination of these (and any other impurities) by

The validation of this method includes a comment about of impurities in the Accuracy section of document DAZT/91/0001 (see Vol. 2.3, page 458), stating that the principal impurities have similar to that of 566C80 (atovaquone) and have been shown to have similar to 566C80 at the wavelength of detection

DRUG PRODUCT – MALARONE Tablets

Only [redacted] is named as an impurity in the MALARONE specification in Section E2.1 (see Vol. 3, page 29).

The [redacted] method given in Section E4.3.5 (see Vol. 3, page 61) applies a [redacted]

The validation of this method in Section E5.3.2 (see Vol. 3, page 116) records the determination of this [redacted] atovaquone.

MEMORANDUM OF TELEFACSIMILE

DATE: April 13, 1999

TO: Tom Shumaker, Regulatory Affairs

APPLICANT: Glaxo Wellcome

FROM: Mary Dempsey, Regulatory Project Manager

THROUGH: Robert Hopkins, M.D., M.P.H., T.M., Medical Team Leader
Andrea Meyerhoff, M.D., M.Sc., DTMH, Medical Officer
Kenneth Hastings, Ph.D., Team Leader Pharmacology/Toxicology
Steve Kunder, Ph.D., Pharmacologist
Leonard Sacks, M.D., Medical Officer
Houda Mahayni, R.Ph., Ph.D., Pharmacokinetic Reviewer
Shukal Bala, Ph.D., Acting Microbiology Team Leader
Norman Schmuff, Ph.D., Chemistry Team Leader
John Smith, Ph.D., Chemist

NDA: 21-078

DRUG: atovaquone and proguanil

Related Documents: Fax dated February 26, 1999
Teleconference of March 11, 1999
Fax dated April 12, 1999

In order to complete the review of your application, please provide answers to the following questions and soon as possible:

BIOPHARM:

1. The initial BE study showed lack of bioequivalence on the lower end of the atovaquone component. The Agency requested a repeat of the study comparing the (1/4) quarter strength to be marketed [redacted] product and the (1/4) quarter strength [redacted] product that was used in the clinical trials. The Agency made a request to repeat the BE study in a fax to Glaxo on February 26, 1999 and a telecon on March 11, 1999.
   Please make the Agency aware of your intentions to either repeat the BE study or not.

2. Please provide the following: Raw data in Electronic Format (ASCII) for the Population PK study entitled: Population Pharmacokinetics of Proguanil in Acute *P.falciparum* Malaria Patients.
3. Please provide the following reference:
   Goodwin L., Whiteman P., Holdich T., et al., The dose-

Escalating pharmacokinetics and clinical acceptability of single dose oral 566C80 in non-patient volunteers. BDPS/90/0001; April 1991.

PHARMACOLOGY/TOXICOLOGY:

4. There was fax to Glaxo, dated February 26, 1999 requesting a comparison of effects observed in toxicology studies with proguanil and previous toxicology studies conducted with related products such as trimethoprim, methotrexate, and pyrimethamine.
   Please provide this information as soon as possible.

5. The Agency had requested that Glaxo send us a listing of the pharm/tox studies by type and date of submission to the IND/NDA.
   Please provide this information as soon as possible.

MICROBIOLOGY:

6. It is stated on page 6 (section C) of submission BZ dated 3/31/99 that "the conclusion that these (proguanil/cycloguanil) are dihydrofolate reductase inhibitor is based on a review of the literature." It should be noted that the literature submitted in the NDA includes review articles only. *Please submit the original papers showing the activity of proguanil/cycloguanil against DHFR.* It should also be noted that some of the recent reports in the literature such as the study by Fidock et al., 1998 (Mol. Pharmacol. 54: 1140) suggest that the mode of action of cycloguanil may be distinct from that of proguanil.

7. Please provide the following information included in the NDA (volume 58, page 46 - 47):

a) The method by which in vitro susceptibility was measured.
b) The basis of calculating chloroquine resistance threshold to be
It should be noted that in the study by Basco et al., 1995 (Am. J. Trop. Med. Hyg. 53: 388) the IC_{50} values for chloroquine susceptible strains were in the range of 20.3 - 31.0 nM (geometric mean 25.1 nM) and that of chloroquine resistant strains 163 - 236 nM (geometric mean 195 nM).

CHEMISTRY:

8. The Agency sent a fax to Glaxo on April 12, 1999 that outlined the reason that the CDER Nomenclature Committee has not approved the drug name MALARONE.
   Please let us know your plans for the name of the drug as soon as possible.

9. Please let the Agency know your plans for proguanil regarding the USAN name.

CLINICAL:

10. Please provide additional information concerning the 120 day safety update. Are there CRFs available?

In order to complete the review process, it is important that these questions be answered as soon as possible. If you need clarification on any issue or wish to have a teleconference, please contact the Regulatory Project Manager, Mary Dempsey, 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

Division of Special Pathogens and Immunologic Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: April 12, 1999 — Number of Pages (including cover sheet): 2
TO: Tom Shumaker
COMPANY: Glaxo Wellcome
FAX NUMBER: 919-483-5756
MESSAGE: RE:
Information concerning nomenclature

NOTE: We are providing the attached information via telefacsimile 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.

FROM: Mary Dempsey
TITLE: Regulatory Project Manager

TELEPHONE: (301) 827-2127 — FAX NUMBER:(301) 827-2475

cc: Division File
NDA 21-078
590/Chem Tl [S]
590/Chem
590/PM [S]

MODE = MEMORY TRANSMISSION START=APR-12 13:41 END=APR-12 13:42

FILE NO.= 142

STN NO.	COM	ABBR NO.	STATION NAME/TEL.NO.	PAGES	DURATION
001	OK	8	919194835756	002/002	00:00'36"

-FOOD & DRUG ADMIN.

********** - - ***** - 301 827 2474- *********

DEPARTMENT OF HEALTH & HUMAN SERVICES *Public Health Service*

Division of Special Pathogens and Immunologic Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: April 12, 1999 Number of Pages (including cover sheet): 2
TO: Tom Shumaker
COMPANY: Glaxo Wellcome
FAX NUMBER: 919-483-5756
MESSAGE: RE:

Information concerning nomenclature

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FROM: Mary Dempsey
TITLE: Regulatory Project Manager

TELEPHONE: (301) 827-2127 FAX NUMBER:(301) 827-2475

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Division of Special Pathogens and Immunologic Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: April 7, 1999 Number of Pages (including cover sheet): 2
TO: Tom Shumaker
COMPANY: Glaxo Wellcome
FAX NUMBER: 919-483-5756
MESSAGE: RE: NDA 21-078
Information Request

NOTE: We are providing the attached information via telefacsimile 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.

FROM: Mary Dempsey
TITLE: Regulatory Project Manager

TELEPHONE: (301) 827-2127 FAX NUMBER:(301) 827-2475

MODE = MEMORY TRANSMISSION START=APR-07 10:41 END=APR-07 10:42

FILE NO.= 092

STN NO.	COM	PEER NO.	STATION NAME/TEL.NO.	PAGES	DURATION
001	OK	8	919194835756	002/002	00:00'58"

-FOOD & DRUG ADMIN.

********** - ***** - 301 827 2474- *********

DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Division of Special Pathogens and Immunologic Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: April 7, 1999 Number of Pages (including cover sheet): 2
TO: Tom Shumaker
COMPANY: Glaxo Wellcome
FAX NUMBER: 919-483-5756
MESSAGE: RE: NDA 21-078
Information Request

NOTE: We are providing the attached information via telefacsimile 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.

FROM: Mary Dempsey
TITLE: Regulatory Project Manager

TELEPHONE: (301) 827-2127 FAX NUMBER:(301) 827-2475

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEFACSIMILE

TO: Tom Shumaker, Regulatory Affairs

FROM: Mary Dempsey, Regulatory Project Manager

THROUGH: Houda Mahayni, R.Ph., Ph.D., Clin. Pharm. & Biopharmaceutics Reviewing Officer

DRUG: Malarone (atovaquone/proguanil)

NDA: 21-078

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

SUBJECT: Information Request for electronic format

The Biopharm reviewer has the following request concerning the electronic components of your submitted NDA 21-078 for Malarone:

Please, if possible, provide the following studies (text and tables) in Word:

115-133
115-132
MALB1002
MALB1004
115-123
BLVS/96/0003
BLVS/96/0004
MALB3001
MALB3003.

Please notify the Division as soon as possible of your ability to fulfill this request.

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.

151

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

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Special Pathogens and Immunologic Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: March 30, 1999 Number of Pages (including cover sheet): 5
TO:
COMPANY:
FAX NUMBER:
MESSAGE: RE: Chemistry Comments regarding DMF

NOTE: We are providing the attached information via telefacsimile 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.

FROM: Mary Dempsey
TITLE: Regulatory Project Manager

TELEPHONE: (301) 827-2127 FAX NUMBER:(301) 827-2475

cc: Division file for NDA 21-078
NDA 21-078
590/ChemTL
590/Chem1
590/PM1

********** -COMM. JOURNAL- ********** DATE MAR-30-1999 ***** TIME 08:18 *** P.01

MODE = MEMORY TRANSMISSION START=MAR-30 08:15 END=MAR-30 08:18

FILE NO.= 218

STN NO.	JOB	ABBR.NO.	STATION NAME/TEL.NO.	PAGES	DURATION
001	OK	8	916097991176	005/005	00:02'29"

-FOOD & DRUG ADMIN.

********** ****** - 301 827 2474- *********

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Special Pathogens and Immunologic Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: March 30, 1999 Number of Pages (including cover sheet): 5
TO:
COMPANY:
FAX NUMBER:
MESSAGE: RE: Chemistry Comments regarding ; DMF

NOTE: We are providing the attached information via telefacsimile 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.

FROM: Mary Dempsey
TITLE: Regulatory Project Manager

TELEPHONE: (301) 827-2127 FAX NUMBER:(301) 827-2475

U.S. Regulatory Affairs - Glaxo Wellcome Inc.

Facsimile Transmission

TO: Ms. Mary Dempsey	DATE: March 5, 1999
COMPANY: DSPIDP, CDER, FDA	FAX NO.: 9-1-301-827-2520
TOTAL NO. OF PAGES: 10	PHONE NO.:

MESSAGE: NDA 21-078

Ms. Dempsey,

Attached is a copy of the November 24, 1997 submission to the Malarone IND —, a summary of the results of the 6-month dog study. Also attached is an updated chart showing the status of the ongoing and planned non-clinical studies. We are continuing to work on an updated analysis of the results seen in the rat and dog repeat-dose studies.

Please contact me at 919-483-9324 regarding this information and for any additional questions concerning Malarone.

Thank you very much,

Tom Shumaker

Tom Shumaker

FROM:

Thomas Shumaker
US Regulatory Affairs
Glaxo Wellcome Inc.
5 Moore Drive
Research Triangle Park
North Carolina 27709

Phone: (919) 483-9324
Fax: (919) 483-5756

DISTRIBUTE COPIES TO:

NDA Pharm/Tox reviewers
Others, as appropriate

GlaxoWellcome

November 24, 1997

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

Re: IND ——MALARONE (atovaquone and proguanil hydrochloride) Tablets for the prophylaxis of malaria
Information Amendment: Nonclinical
Results of 6-Month Dog Study
Serial No.: 014

Dear Dr. Goldberger:

We are amending the above referenced Investigational New Drug Application to provide the recently available summary of results from the following toxicology study report:

> **A Six Month Oral Toxicology Study In Beagle Dogs Given Atovaquone and Proguanil Alone Or In Combination**

The final study reports for this study as well as the 6-month rat toxicology study are in final preparation. These results from the dog study are provided for your information in advance of the submission of the final reports in the upcoming Malarone NDA.

This submission will be made in triplicate, with an additional desk copy being provided directly to Ms. Pauline Fogarty. Please contact me at (919) 483-9324 should you have any comments or questions regarding this submission.

Sincerely,

Thomas K. Shumaker
Manager, Regulatory Affairs

Glaxo Wellcome Research and Development
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709
Telephone
919 248 2100
A Division of
Glaxo Wellcome Inc.

Summary: A Six Month Oral Toxicology Study In Beagle Dogs Given Atovaquone and Proguanil Alone Or In Combination

Introduction:

A 6 month combination study with atovaquone and proguanil in the dog produced mortalities, clinical signs of toxicity, hematology findings and lesions in a number of organs. The significant findings were all attributable to the action of proguanil since no significant changes were present in animals receiving the high dose of atovaquone alone. Histopathological changes previously observed in a 1 month combination study in the dog included maturation arrest enteritis, haemopoietic depletion, and renal tubular necrosis with dilatation and regeneration. The changes encountered in the 6 month combination study are described below.

Study Design:

Atovaquone and proguanil were administered alone or in combination by oral gavage to Beagle dogs for up to 27 weeks. The study design was as follows:

Group	Dose (mg/kg/day)[a]		Numbers of animals	
	Atovaquone	Proguanil	Male	Female
1 Control	0	0	6[b]	6[b]
2 Low combination	10	4	4	4
3 Mid combination	20	8	4	4
4 High combination	30	12	6[b]	6[b]
5 High Atovaquone	30	0	6[b]	6[b]
6 High Proguanil	0	12	6[b]	6[b]

[a] Initial doses of 50mg/kg/day atovaquone and 20mg/kg/day proguanil alone or in combination were given to dogs in Groups 4, 5 or 6 but were reduced to 40mg/kg/day atovaquone and 16mg/kg/day proguanil during Weeks 5 to 9 and further reduced to 30mg/kg/day atovaquone and 12mg/kg/day proguanil during Weeks 10 to 26.

[b] 2 animals were allocated to recovery

Results

MORTALITIES: Three Group 4 dogs and four Group 6 dogs were found dead or were euthanized *in extremis* between Days 40 and 170.

CLINICAL OBSERVATIONS: Emesis and salivation were frequently observed in animals in Groups 4 and 6, throughout the study. Altered feces (including liquid and soft) were noted for animals in Groups 3,4 or 6. The most severe occurrences were in the groups receiving the highest doses of proguanil.

BODYWEIGHT AND FOOD CONSUMPTION: Lower bodyweight, weight loss and decreased food intake were generally seen for animals in Groups 4 and 6 during the first month of dosing. Bodyweights, weight gain and food intake became comparable to the vehicle control group following the first reduction of the dose levels to 40mg atovaquone/kg/day and 12mg proguanil/kg/day, except for the males in Group 4, which generally remained lower than control group values.

ELECTROCARDIOGRAPHIC EXAMINATIONS: At week 26, two Group 5 females (atovaquone alone) showed a single, interpolated ventricular extrasystole. One of these females and a Group 4 female exhibited notched P waves and one Group 6 female showed sinus tachycardia. These changes can occur spontaneously and therefore the significance is equivocal. Variable ST-T configuration was noted in the Group 6 female euthanized *in extremis*.

HEMATOLOGY: Slight reduction in red blood cell count was noted at week 4 in animals in Groups 3, 4 and 6. Recovery was noted thereafter following the reduction of dose levels.

MACROSCOPIC FINDINGS: Gross findings observed were generally limited to the animals in Groups 4 and 6 and included emaciation, dark/raised areas, thickening or mass in the right atrium of the heart, dark foci/areas in the gall bladder, depressed areas in the duodenum and jejunum.

HISTOPATHOLOGICAL FINDINGS

Treatment with proguanil either alone or in combination with atovaquone resulted in significant microscopic changes in the heart, liver, gall bladder, kidneys, lungs and lymphoid system in both males and females. Some of these findings were present ~~in some~~ animals from all groups dosed with proguanil. After a 4 week recovery period some of these findings were still present.

Heart

A cardiac lesion defined as fibrovascular proliferation was observed only in dogs receiving high dose proguanil either alone or in combination with atovaquone (Groups 4 and 6). This was essentially a chronic inflammatory process localised to the right atrium and in some animals was graded as severe (and correlated with the presence of a mass at necropsy). The incidence and severity in decedent, terminal and recovery animals is shown in Table 1 in Appendix 1.

Liver and Gall Bladder

In dogs receiving proguanil either alone or in combination with atovaquone bile duct hyperplasia was present in some animals from all dose groups. Lesions in the gall bladder, described as mucosal atrophy with or without inflammation and pigment accumulation, were also present in some animals from all dose groups receiving proguanil (See Table 2 in Appendix 2).

Kidney

Slight to moderate pyelitis was present predominantly in decedent animals; 1 male and 1 female from Group 4, and in 1 female from Group 6. One terminal female from Group 6 also had slight pyelitis.

Mild pyelonephritis was present in 1 decedent male and in 1 terminal female from Group 6. Severe pyelonephritis was present in 1 terminal male from Group 3.

Severe interstitial nephritis was present in 1 terminal female from Group 4 and although the aetiology of this lesion was not clear, it was associated with papillary atrophy which suggests that ascending infection may also have been present.

There were no renal effects seen in Group 2, nor in any group at the termination of the 4 week drug-free recovery period.

Lymphoid System

Increased severity of thymic atrophy and the occurrence of lymphoid atrophy in the spleen or lymph nodes were observed in some animals receiving high dose proguanil either alone (Group 6) or in combination with atovaquone (Group 4). More severe thymic atrophy occurred predominantly in decedent animals, although one terminal female from both Group 4 and Group 6 also showed thymic atrophy. Lymphoid atrophy in the spleen and lymph nodes occurred only in decedent animals.

None of these findings were present in recovery animals.

Lungs

Interstitial pneumonia was present in both control and treated animals, but the lesions appeared to be more severe in animals in Groups 3, 4 and 6. Bronchiolitis or bronchopneumonia were also present in some animals but no dose-related effect was apparent.

Some recovery was evident after a 4 week period, but was incomplete.

Additional Findings

In one terminal female receiving proguanil alone (Group 6) there was slight multifocal necrosis with haemorrhage in the brain.

Bone marrow hypocellularity and gastritis/enteritis were present in decedent animals only.

Discussion

The various findings described above were all attributable to the action of proguanil (either alone or in combination with atovaquone) since no significant findings occurred in the group receiving a high dose of atovaquone alone.

The lesions observed in the heart were typical of those induced by a number of pharmaceutical agents (potassium channel openers, phosphodiesterase inhibitors) where the lesion in the dog is consistently localised to the right atrium. The aetiology of this lesion is unclear. Experience with other pharmaceutical agents suggests that this lesion can be induced in a relatively short period of time and progresses with continued treatment. It should be noted, however, that no such lesions were present in a 1 month study with proguanil and atovaquone in the dog at higher doses. In this study the earliest timepoint at which atrial lesions were observed was Day 147 although they were well-advanced at this time.

Electrocardiography did not predict cardiac lesions and in all except one animal where changes were present in ECGs, no histopathological lesions were seen. The ECG changes described for animals in Group 5 receiving 30 mg/kg/day of atovaquone alone were of equivocal significance

since earlier studies in the dog with doses up to 500 mg/kg/day for up to 1 year showed no ECG changes.

Biliary hyperplasia in the liver is a commonly encountered spontaneous finding in the Beagle dog, but the lesion encountered in this study was unusual in that it was focal and consistently localised to the tip of one liver lobe in those dogs least affected. More advanced lesions were more diffuse in nature and were accompanied by significant fibrosis. Mucosal atrophy in the gall bladder is uncommon in untreated Beagle dogs and the changes in this study showed a clear relationship to treatment.

The incidence and severity of typical background pathology in the lungs of dogs, both control and treated, in this 6 month study were unusually high. Although treatment appeared to exacerbate these lesions, particularly with regard to the severity of alveolar epithelial hyperplasia, this is not likely to represent direct toxicity.

The following table shows the comparative exposures to proguanil and atovaquone when administered to humans, dogs and rats. Although a clear no-effect level was not present in the dog study at the lowest dose where slight changes were noted in the liver and gallbladder, exposure to proguanil at this dose was approximately 3 times the clinical exposure to proguanil in humans. It should also be noted that in the rat 6 month combination study treatment-related effects were limited to the cecum where mucosal hyperplasia was seen at all doses.

In conclusion, given the potential risks associated with exposure to malaria, we believe that the above findings in this 6 month dog study do not preclude the use of atovaquone and proguanil in combination for treatment or prophylaxis of malaria. The average duration of treatment for malaria prophylaxis is 4 weeks. Proguanil has been extensively used for malaria prophylaxis since the 1940s and has a long history of safe and effective use in humans. Proguanil has been considered the safest of the antimalarial agents and is now often used in combination with other antimalarials due to decreasing efficacy of monotherapy.

COMPARISON OF EXPOSURES AND DOSES BETWEEN MAN, DOG AND RAT WHEN ADMINISTERED ATOVAQUONE AND PROGUANIL AT A RATIO OF 2.5 TO 1.

	Doses of Atovaquone: Proguanil	AUC in hr.µg/ml for Atovaquone	AUC in hr.µg/ml for Proguanil	AUC in hr.µg/ml for Cycloguanil	Multiple of Proguanil exposure compared to human exposure
Human	250:100 mg	50	0.6432	0.26	
Dog [a]	10:4 mg/kg	50 - 64	2.0 - 2.3	0.2-0.4	x 3.3
	20:8 mg/kg	52 - 49	5.8 - 6.2	1.2-1.4	x 9.3
	30:12 mg/kg	79 - 93	8.3 - 9.2	1.5-2.0	x 13.6
Rat [a]	10:4 mg/kg	392 - 547	0.081 - 0.099	LLOQ[b]	x 0.1
	20:8 mg/kg	642 - 765	0.202 - 0.250	LLOQ[b]	x 0.4
	50:20 mg/kg	1313 - 1642	0.905 - 0.939	LLOQ[b]	x 1.4

[a] 6 month study data

[b] Below the lower level of quantification (LLOQ)

Appendix 1

Table 1 Incidence of microscopic changes in the heart in all animals

	Decedents				Terminal				Recovery			
	Proguanil 12 mg/kg/day 566C80 30 mg/kg/day		Proguanil 12 mg/kg/day		Proguanil 12 mg/kg/day 566C80 30 mg/kg/day		Proguanil 12 mg/kg/day		Proguanil 12 mg/kg/day 566C80 30 mg/kg/day		Proguanil 12 mg/kg/day	
	M	F	M	F	M	F	M	F	M	F	M	F
Number of animals	2	1	3	1	2	3	1	3	2	2	2	2
Heart												
Fibrovascular proliferation												
slight	-	-	-	1	1	-	-	-	-	-	-	-
moderate	-	-	1	-	1	2	-	1	-	-	-	1
severe	1	-	-	-	-	-	-	1	-	-	1	-
Endocarditis												
slight	1	-	-	-	-	-	-	-			-	

Appendix 2

Table 2 Incidence of microscopic changes in the liver and gall bladder of animals dying or euthanized during the dosing phase of the study

Decedents	Proguanil 12 mg/kg/day 566C80 30 mg/kg/day		Proguanil 12 mg/kg/day	
	M	F	M	F
Number of animals	2	1	3	1
Liver				
Biliary hyperplasia				
slight	2	-	1	-
Gall Bladder				
Mucosal atrophy				
slight	2	-	1	1
mild	-	1	1	-

Incidence of microscopic changes in the liver and gall bladder of animals euthanized at the end of the dosing phase of the study

Terminal	Proguanil 4 mg/kg/day 566C80 10 mg/kg/day		Proguanil 8 mg/kg/day 566C80 20 mg/kg/day		Proguanil 12 mg/kg/day 566C80 30 mg/kg/day		566C80 30 mg/kg/day		Proguanil 12 mg/kg/day	
	M	F	M	F	M	F	M	F	M	F
Number of animals	4	4	4	4	2	3	4	4	1	3
Liver										
Biliary hyperplasia										
slight	1	1	2	1	2	1	-	-	-	-
mild	-	-			-	1	-	-	-	2
moderate	-	-	-	-	-	-	-	-	-	1
Gall Bladder										
Mucosal atrophy										
slight	-	2	4	3	2	3	-	-	1	2
mild	-	-	-	1	-	-	-	-	-	-
moderate	-	-	-	-	-	-	-	-	-	1

Incidence of microscopic changes in animals euthanized at the end of a 4 week recovery period without dosing

Recovery	Proguanil 12 mg/kg/day 566C80 30 mg/kg/day		Proguanil 12 mg/kg/day	
	M	F	M	F
Number of animals	2	2	2	2
Liver				
Biliary hyperplasia				
slight	2	-	-	1
Gall Bladder				
Mucosal atrophy				
slight	2	2	2	2

NDA 21-078
Malarone Tablets

Agreements reached between the Division and Glaxo Wellcome regarding the commitment to conduct Reprotoxicity and Carcinogenicity studies

Nonclinical Reproductive Toxicology Studies

Glaxo Wellcome agrees with the Agency that Segment I and III reproductive toxicity studies should be performed. In line with the Agency comments as reflected in the October 6, 1997 facsimile, we are conducting these studies with proguanil hydrochloride as Phase IV commitments, according to the following schedule:

Study	Proposed Start Date (Actual Start Date)	Proposed Date of Non-QA'd Study Report	Proposed Date of Final QA'd Study Report
Fertility Study In Rats (Segment I)			
Pre and Post natal developmental Study in Rats (Segment III)			

Nonclinical Carcinogenicity Studies

Glaxo Wellcome also agrees with the Agency that Malarone Tablets might be used for six months or longer in duration or could be subject to chronic intermittent use during the lifetime for some patients. Therefore, we have concluded that additional studies would be appropriate to fulfill these requirements. We are conducting these studies with proguanil hydrochloride as Phase IV commitments, according to the following schedule:

Study	Proposed Start Date (Actual Start Date)	Proposed Date of Non-QA'd Study Report	Proposed Date of Final QA'd Study Report
90 Day Pre-oncogenicity Study In Mice			
Carcinogenicity Study in Mice			
Carcinogenicity Study in Rats			

In view of the demonstrated toxicity of proguanil in animals, the exposures to proguanil in these long term studies are expected to provide only minimal safety ratios when compared to humans.

U.S. Regulatory Affairs - Glaxo Wellcome Inc.

Facsimile Transmission

TO: Ms. Mary Dempsey	DATE: March 4, 1999
COMPANY: DSPIDP, CDER, FDA	FAX NO.: 9-1-301-827-2520
TOTAL NO. OF PAGES: 2	PHONE NO.:

MESSAGE: NDA 21-078

Ms. Dempsey,

Attached is a chart showing the location of the Declaration of Helsinki statements for the Phase II/III clinical efficacy trials in the Malarone NDA. Please let me know if this list does not sufficiently address your needs.

Please contact me at 919-483-9324 regarding this list and for any additional questions concerning Malarone.

Thank you very much,

Tom Shumaker

FROM:

Thomas Shumaker
US Regulatory Affairs
Glaxo Wellcome Inc.
5 Moore Drive
Research Triangle Park
North Carolina 27709

Phone: (919) 483-9324
Fax: (919) 483-5756

DISTRIBUTE COPIES TO:

NDA 21-078
Malarone (atovaquone and proguanil hydrochloride) Tablets

Declaration of Helsinki statement

Treatment Studies
The Declaration of Helsinki statement for the protection of the rights of human subjects engaged in clinical trials can be found in Subsection 4.3.2 Ethics of Section 4.3 Management of the individual treatment study reports and in Section 5 Ethics of the protocols for each Phase III study. The exact location for each is given below:

Treatment Studies	NDA Volume	NDA Page
115-005 Study Report	44	38
115-012 Study Report	46	20
115-120 Study Report	47	21
Protocol	47	56
115-122 Study Report	48	21
Protocol	48	75
115-127 Study Report	49	19
Protocol	49	57
115-130 Study Report	50	20
Protocol	50	70
115-131 Study Report	51	21
Protocol	51	87
115-134 Study Report	52	21
Protocol	52	81
115-135 Study Report	53	20
Protocol	53	52
115-136 Study Report	54	21
Protocol	54	63
115-123 Study Report	55	20
Protocol	55	53

Prophylaxis Studies

The Declaration of Helsinki statement for the protection of the rights of human subjects engaged in clinical trials can be found in the Ethics Sections of the protocols for each Phase II/III study. The exact location for each study report is given below:

Prophylaxis Studies	NDA Volume	NDA Page
MALB2001 Protocol	58	349
MALB3001 Protocol	61	250
MALB3003 Protocol	64	44
MALB3002 Protocol	67	205

MAR - 5 1999

U.S. Regulatory Affairs - Glaxo Wellcome Inc.

Facsimile Transmission

TO: Ms. Mary Dempsey DATE: March 3, 1999
COMPANY: DSPIDP, CDER, FDA FAX NO.: 9-1-301-827-2520
TOTAL NO. OF PAGES: 2 PHONE NO.:

MESSAGE: NDA 21-078

Ms. Dempsey,

Attached is a proposal for conversion of the tables in the summary clinical documents of the NDA to MS Word format. Please circulate this to the affected NDA reviewers and let us know if this approach will sufficiently address their needs.

Please contact me at 919-483-9324 regarding this proposal and for any additional questions concerning Malarone.

Thank you very much,

Tom Shumaker

FROM:
Thomas Shumaker
US Regulatory Affairs
Glaxo Wellcome Inc.
5 Moore Drive
Research Triangle Park
North Carolina 27709

Phone: (919) 483-9324
Fax: (919) 483-5756

DISTRIBUTE COPIES TO:

NDA Review team

Proposal for Conversion of Tables in Summary Documents to MS Word Format

Glaxo Wellcome is sensitive to the request from the reviewers of the Malarone Tablets NDA for tables, in MS Word format, from the Summary, ISE, and ISS documents that were initially delivered in Adobe PDF format.

To meet this need, Glaxo Wellcome proposes to provide files containing these tables in MS Word format, on diskette.

Glaxo Wellcome will convert the tables from their native Interleaf format to MS Word format and will verify that the content of these tables matches the paper copy, submitted in the Original NDA, prior to delivery to the FDA. We will also ensure that table titles and file naming conventions adequately facilitate table identification. Please be advised that minor changes in fonts or point sizes may occur during our file conversion activities, therefore, the appearance of the MS Word tables may not be identical to the hardcopy or paper version, however, the content will be verified, as stated above.

We expect to be able to complete the conversion and verification of the tables in the documents listed below by **March 12, 1999**. We are not proposing, at this time, to convert the tables from the individual treatment and prophylaxis study reports. We can discuss this further if tables from specific individual study reports are required.

Documents proposed for conversion of tables to MS Word:

- Item 3 Summary
- ISE Treatment
- ISS Treatment
- ISS Prophylaxis (ISE Prophylaxis ?)
- ISS Prophylaxis

If you have any questions regarding this proposal or require additional information, please contact me at 919-483-9324.

Sincerley,

Thomas K. Shumaker

Thomas K. Shumaker
Project Director
Regulatory affairs

U.S. Regulatory Affairs - Glaxo Wellcome Inc.

Facsimile Transmission

TO: Ms. Mary Dempsey
DATE: February 18, 1999
COMPANY: DSPIDP, CDER, FDA
FAX NO.: 9-1-301-827-2520
TOTAL NO. OF PAGES: 2
PHONE NO.:

MESSAGE: NDA 21-078

Ms. Dempsey,

Attached is a cross reference table giving the page location for each of the documents provided electronically in pdf format for the Malarone NDA. This was not too difficult to generate, so I thought that I would send this up as soon as we had it.
I hope that you and the other reviewers find this useful.

We are working on the other requests.

Please contact me at 919-483-9324 regarding any additional questions concerning Malarone.

Thank you very much,

Tom Shumaker

FROM:
Thomas Shumaker
US Regulatory Affairs
Glaxo Wellcome Inc.
5 Moore Drive
Research Triangle Park
North Carolina 27709

Phone: (919) 483-9324
Fax: (919) 483-5756

DISTRIBUTE COPIES TO:
NDA Review team

NDA 21-078
MALARONE (atovaquone and proguanil hydrochloride) Tablets

Cross-reference page listing of documents provided electronically in pdf format

(Use "View →Go To Page ..." function or click on page counter box at bottom of Acrobat Reader screen)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Special Pathogens and Immunologic Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: February 16, 1999 Number of Pages (including cover sheet): 2
TO: Tom Shumaker
COMPANY: Glaxo Wellcome
FAX NUMBER: 919-483-5756
MESSAGE: RE: Information Request for NDA 21-078

NOTE: We are providing the attached information via telefacsimile 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.

FROM: Mary Dempsey
TITLE: Project Manager

TELEPHONE: (301) 827-2127 FAX NUMBER:(301) 827-2475

MODE = MEMORY TRANSMISSION START=FEB-16 15:42 END=FEB-16 15:47

FILE NO.= 228

STN NO.	COM	ABBR NO.	STATION NAME/TEL.NO.	PAGES	DURATION
001	OK	8	919194835756	002/002	00:00'57"

-FOOD & DRUG ADMIN.

********** - - ***** - 301 827 2474- **********

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Special Pathogens and Immunologic Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: February 16, 1999 Number of Pages (including cover sheet): 2
TO: Tom Shumaker
COMPANY: Glaxo Wellcome
FAX NUMBER: 919-483-5756
MESSAGE: RE: Information Request for NDA 21-078

NOTE: We are providing the attached information via telefacsimile 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.

FROM: Mary Dempsey
TITLE: Project Manager

TELEPHONE: (301) 827-2127 FAX NUMBER:(301) 827-2475

GlaxoWellcome FACSIMILE

DATE	JANUARY 14, 1999	TOTAL PAGES	2
TO	Ms. Mary Dempsey Food and Drug Administration	FAX PHONE	(301) 827-2475 (301) 827-2127
FROM	Ms. Kimberley Jessup-Crippen	FAX PHONE	(919) 483-5381 (919) 483-9804

Re: **NDA 21-078; MALARONE™ (atovaquone and proguanil hydrochloride) Tablets for the Treatment and Prevention of Malaria**
Response to FDA Request/Comment: CMC

The following information is provided in response to the telefacsimile sent on January 14, 1999.

Question 1 regarding the list of sites:

- In addition to the manufacture of the drug substance proguanil hydrochloride, [redacted], is also responsible for quality control, bulk packaging and stability testing of proguanil hydrochloride.
- In addition to the functions listed for the Glaxo Wellcome site in Mississauga, Canada, this site is also responsible for the quality control of MALARONE and MALARONE Pediatric Tablets.
- The full name and address for the Dartford facility is:

  Glaxo Wellcome Operations
  The Wellcome Foundation Ltd
  Temple Hill
  Dartford
  Kent DA1 5AH
  UK

Glaxo Wellcome Inc.
Five Moore Drive
PO Box 13398
Research Triangle Park, NC
27709-3398

U. S. Regulatory Affairs
Phone 919-483-2100

- Glaxo Wellcome Research and Development located at Park Road, Ware, Hertfordshire SG12 0DP, UK, is the development site at which stability testing for some of the NDA DP batches was performed. Glaxo Wellcome Operations UK Ltd, Priory Street, Ware, is the commercial facility and was not used as a site for NDA DP stability testing.
- Glaxo Wellcome will follow up on separate cover information regarding CFNs for the Glaxo Wellcome sites and the contract-testing lab [redacted]. The CFN for [redacted] however, has been confirmed as being correct.

Question 2 regarding approved sites of manufacture for the drug substance atovaquone:

- Information regarding the manufacture of atovaquone drug substance is contained in NDA 20-259 for MEPRON® Tablets and all supplements thereto. The address of the approved manufacturer for atovaquone is:

  Glaxo Wellcome Operations
  The Wellcome Foundation
  Temple Hill
  Dartford
  Kent DA1 5AH
  UK
- The site registration number for this facility is FCUK 685.
- In addition to the information provided in the NDA and subsequent supplements, information on the buildings and facilities may be found in DMF [redacted].

Should you have any additional questions, please do not hesitate to contact me at the numbers provided or page me at (888) 361-4169.

Sincerely

Kimberley Jessup-Crippen
US CMC Submissions
Chemistry Pharmacy and Manufacturing Regulatory Affairs and Quality Division

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Special Pathogens and Immunologic Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: January 26, 1999 Number of Pages (including cover sheet): 3
TO: Tom Shumaker
COMPANY: Glaxo Wellcome
FAX NUMBER: 919-483-5756
MESSAGE: RE: NDA 21-078, Malarone
Information Request

NOTE: We are providing the attached information via telefacsimile 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.

FROM: Mary Dempsey
TITLE: Project Manager

TELEPHONE: (301) 827-2127 FAX NUMBER:(301) 827-2475

cc: Division file
NDA 21-078
590/MOT
590/PM

MODE = MEMORY TRANSMISSION START=JAN-26 08:51 END=JAN-26 08:52

FILE NO.= 215

STN NO.	COM	ABBR NO.	STATION NAME/TEL.NO.	PAGES	DURATION
001	OK	8	919194835756	003/003	00:00'49"

-FOOD & DRUG ADMIN.

********** ***** 301 827 2474- *********

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Special Pathogens and Immunologic Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: January 26, 1999 Number of Pages (including cover sheet): 3
TO: Tom Shumaker
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FAX NUMBER: 919-483-5756
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FROM: Mary Dempsey
TITLE: Project Manager

TELEPHONE: (301) 827-2127 FAX NUMBER:(301) 827-2475

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Division of Special Pathogens and Immunologic Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: January 14, 1999 Number of Pages (including cover sheet): 4
TO: Tom Shumaker, Regulatory Affairs
COMPANY: Glaxo Wellcome
FAX NUMBER: 919-483-5756
MESSAGE: RE: Chemistry Information Request
Please respond ASAP by fax.

NOTE: We are providing the attached information via telefacsimile 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.

FROM: Mary Dempsey
TITLE: Project Manager

TELEPHONE: (301) 827-2127 FAX NUMBER:(301) 827-2475

cc: Division file
NDA 21-078
590/Chem/: LT
590/Chem TL: LT
590/PM/[redacted]
3 LT

MODE = MEMORY TRANSMISSION START=JAN-14 09:26 END=JAN-14 09:30

FILE NO.= 096

STN NO.	COM	ABBR NO.	STATION NAME/TEL.NO.	PAGES	DURATION
001	OK	8	919194835756	004/004	00:00'59"

-FOOD & DRUG ADMIN.

********** - - ***** - 301 827 2474- **********

DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Division of Special Pathogens and Immunologic Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: January 14, 1999 Number of Pages (including cover sheet): 4
TO: Tom Shumaker, Regulatory Affairs
COMPANY: Glaxo Wellcome
FAX NUMBER: 919-483-5756
MESSAGE: RE: Chemistry Information Request
Please respond ASAP by fax.

NOTE: We are providing the attached information via telefacsimile 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.

FROM: Mary Dempsey
TITLE: Project Manager

TELEPHONE: (301) 827-2127 FAX NUMBER:(301) 827-2475

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JAN 6 1999

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

Dear Mr. Shumaker:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: MALARONE (atovaquone and proguanil hydrochloride) Tablets

Therapeutic Classification: Priority (P)

Date of Application: December 29, 1998

Date of Receipt: December 29, 1998

Our Reference Number: 21-078

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 12, 1999 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 29, 1999.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Division Document Room
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

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

Sincerely,

LST

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:
Archival NDA 21-078
HFD-590/Div. Files
HFD-590/M.Dempsey
DISTRICT OFFICE

Drafted by: mjd/January 5, 1999
Initialed by:
final:
filename: 21-078

ACKNOWLEDGEMENT (AC)