DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-078/S-003

GlaxoSmithKline
Attention: Ms. Debra Hackett
Regulatory Affairs
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101-7929

Dear Ms. Hackett:

Please refer to your supplemental new drug application dated October 5, 2001 received October 9, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Malarone™ (atovaquone and proguanil hydrochoride) Tablets.

We acknowledge receipt of your submissions dated as follows:

October 29, 2001	July 2, 2002
November 29, 2001	July 24, 2002
March 25, 2002	July 30, 2002
June 25, 2002	August 2, 2002

This supplemental new drug application provides for revisions to the Malarone™ package insert to add information related to the pharmacokinetics of Malarone™ in special populations (geriatric, hepatic impairment) and prophylactic use of Malarone™ in non-immune travelers based on data collected to address post marketing study commitments outlined in the July 14, 2000 approval letter.

We have completed the review of this application, 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 enclosed labeling text. Accordingly, this application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling submitted August 02, 2002. Marketing this product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but

no more than 30 days after it is printed. Please individually mount ten of the copies on heavyweight paper or similar material. For administrative purposes, this submission should be designated "**FPL for approved NDA 21-078/S-003"**. Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. 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-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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

Your submission dated October 5, 2001, also reported on the following postmarketing study commitments.

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.

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.

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.

Your submission dated January 11, 2001, reported on the following postmarketing study commitment.

11. Develop a dissolution method that avoids using (b)(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.

We have reviewed your submissions and conclude that the above commitments were fulfilled.

The following commitments listed in our July 14, 2000, letter have not yet been determined to be fulfilled:

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 nonimmune 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-trasmitted *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 250mg atovaquone/100mg 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 (b)----------(b)----------to the UK product (b)---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.

   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 (b)----------to the UK product ((b) 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.

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 breakthrought 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.

If you have any questions, call Michael Bourg, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Acting Director
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Renata Albrecht
8/2/02 03:35:24 PM
NDA 21-078/S-003