DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

NDA 21-078/S-008, S-009

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

Dear Ms. Hackett:

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Malarone® (atovaquone and proguanil hydrochloride) Tablets:

Supplement	Date submitted	Date received
008	August 27, 2004	August 31, 2004
009	November 22, 2004	November 24, 2004

These supplemental new drug applications provide for the following revisions to the package insert (additions are double underlined and deletions are in ~~strikethrough~~):

1. CONTRAINDICATIONS

- The first paragraph was revised to read:

> MALARONE is contraindicated in individuals with known hypersensitivity to atovaquone or proguanil hydrochloride or any component of the formulation. Rare cases ~~1 case~~ of anaphylaxis following treatment with atovaquone/proguanil ~~was observed.~~ have been reported.

2. PRECAUTIONS

- The ***Proguanil*** subsection under **Carcinogenesis, Mutagenesis, Impairment of Fertility** was revised to read**:**

> ~~***Proguanil:*** Carcinogenicity studies with proguanil have not been completed. Proguanil was not genotoxic in in vitro or in vivo studies.~~
> No evidence of a carcinogenic effect was observed in studies conducted in CD-1 mice (doses up to 1.51 times the average systemic human exposure based on AUC) and in Wistar Hannover rats (doses up to 1.12 times the average systemic human exposure).
>
> Proguanil ~~alone~~ was negative with or without metabolic activation in the Ames *Salmonella* mutagenicity assay and the Mouse Lymphoma mutagenesis assay.
> No evidence of genotoxicity was observed in the in vivo Mouse Micronucleus assay.

Cycloguanil, the active metabolite of proguanil, was also negative in the Ames test, but was positive in the Mouse Lymphoma assay and the Mouse Micronucleus assay. These positive effects with cycloguanil, a dihydrofolate reductase inhibitor, were significantly reduced or abolished with folinic acid supplementation.

Genotoxicity studies have not been performed with atovaquone in combination with proguanil. Effects of MALARONE on male and female reproductive performance are unknown.

3. **ADVERSE REACTIONS**

- The following subsection was revised under **Post-Marketing Adverse Reactions**:

Skin/Hypersensitivity: Cutaneous reactions ranging from rash, photosensitivity, angioedema, and urticaria to rare cases of anaphylaxis, erythema multiforme, and Stevens-Johnson syndrome.

We completed our review of these supplemental new drug applications. These applications are approved, effective on the date of this letter for use as recommended in the agreed-upon labeling text (enclosed) and with the minor editorial revisions listed below:

The following sentence in **PRECAUTIONS**, **Carcinogenesis, Mutagenesis, Impairment of Fertility** should be revised to read:

Proguanil: No evidence of a carcinogenic effect was observed in 24-month studies conducted in CD-1 mice (doses up to 1.5~~1~~ times the average systemic human exposure based on AUC) and in Wistar Hannover rats (doses up to 1.1~~2~~ times the average systemic human exposure).

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted draft labeling (package insert submitted November 22, 2004 to NDA 21-078/S-009). These revisions are terms of the approval of these applications.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submission in Electronic Format – NDA*. 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. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions "**FPL for approved supplements NDA 21-078/S-008, S-009**." Approval of these submissions by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-410
FDA
5600 Fishers Lane
Rockville, MD 20857

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

If you have any questions, call Robin Anderson, Labeling Reviewer, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
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

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