**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Food and Drug Administration
Rockville, MD 20857

NDA 21-078/S-002

GlaxoSmithKline
Attention: 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 application dated January 8, 2001, received January 9, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Malarone® (atovaquone and proguanil hydrochloride) Tablets.

We acknowledge receipt of your submissions dated May 6, 2003, March 3, 2004, May 5, 2004 and August 20, 2004.

Your submission of August 20, 2004 constituted a complete response to our April 30, 2003 action letter.

This supplemental new drug application provides for the following revisions to the package insert (additions are double underlined and deletions are in ~~strikethrough~~):

1. **CLINICAL PHARMACOLOGY**
   - The ***Renal Impairment*** subsection was revised to read:

***Renal Impairment:*** ~~In patients with mild to moderate renal impairment, oral clearance and/or AUC data for atovaquone, proguanil, and cycloguanil are within the range of values observed in patients with normal renal function.~~ In patients with mild renal impairment (creatinine clearance 50 to 80 mL/min), oral clearance and/or AUC data for atovaquone, proguanil, and cycloguanil are within the range of values observed in patients with normal renal function (creatinine clearance > 80 mL/min). In patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min), mean oral clearance for proguanil was reduced by approximately 35% compared with patients with normal renal function (creatinine clearance > 80 mL/min) and the oral clearance of atovaquone was comparable between patients with normal renal function and mild renal impairment. No data exists on the use of MALARONE for long term prophylaxis (over 2 months) in individuals with moderate renal failure. In patients with severe renal impairment (creatinine clearance < 30 mL/min), atovaquone $C_{max}$ and AUC are reduced but the elimination half-lives for proguanil and cycloguanil are prolonged, with corresponding increases in AUC, resulting in the potential of drug accumulation and toxicity with repeated dosing (see **CONTRAINDICATIONS**).

## 2. PRECAUTIONS

- The following paragraph was deleted in the **General** subsection:

~~In patients with severe renal impairment (creatinine clearance < 30 mL/min) alternatives to MALARONE should be recommended for treatment of acute *P. falciparum* malaria whenever possible (see CONTRAINDICATIONS and CLINICAL PHARMACOLOGY: Special Populations: Renal Impairment). The concomitant administration of MALARONE and any other medication containing proguanil hydrochloride should be avoided.~~

## 3. ADVERSE REACTIONS

- The following paragraph was revised:

In a third active-controlled study, MALARONE (n = 110) was compared with chloroquine/proguanil (n = 111) for the prophylaxis of malaria in 221 nonimmune pediatric patients (see CLINICAL STUDIES). The mean duration of exposure was 23 days for MALARONE, 46 days for chloroquine, and 43 days for proguanil, reflecting the different recommended dosage regimens for these products. Fewer patients treated with MALARONE reported abdominal pain (2% vs. 7%) or nausea ( < 1% vs. 7%) ~~(b)(4)~~ than children who received chloroquine/proguanil. ~~(b)(4)~~ eams (2% vs. < 1%), and blurred vision (0% vs. 2%) occurred in similar proportions of patients receiving either MALARONE or chloroquine/proguanil, respectively. Two patients discontinued prophylaxis with chloroquine/proguanil due to adverse events, while none of those receiving MALARONE discontinued due to adverse events.

- The following revisions were made to the **Post-Marketing Adverse Reactions** subsection:

***Skin:*** Cutaneous reactions ranging from rash, photosensitivity, and urticaria to rare cases of erythema multiforme and ~~. In addition, one case of~~ Stevens-Johnson syndrome. ~~has been reported~~.

***Central Nervous System:*** Rare cases of seizures and psychotic events (such as hallucinations); however, a causal relationship has not been established.

## 4. OVERDOSAGE

- The first sentence was revised to read:

There is ~~limited information regarding overdosage from the administration of MALARONE.~~ no information on overdoses of MALARONE substantially higher than the doses recommended for treatment.

## 5. DOSAGE AND ADMINISTRATION

- The **Patients with Renal Impairment** subsection was revised to read:

**Patients with Renal Impairment:** MALARONE should not be used for malaria prophylaxis in patients with severe renal impairment (creatinine clearance <30 mL/min).~~, and alternatives to MALARONE should be recommended for treatment of acute *P. falciparum* malaria whenever~~

~~possible (see CONTRAINDICATIONS, PRECAUTIONS: General, and CLINICAL PHARMACOLOGY: Special Populations). No dosage adjustments are needed in patients with mild to moderate renal impairment.~~

MALARONE may be used with caution for the treatment of malaria in patients with severe renal impairment (creatinine clearance < 30 mL/min), only if the benefits of the 3-day treatment regimen outweigh the potential risks associated with increased drug exposure (see **CLINICAL PHARMACOLOGY: Special Populations: Renal Impairment**). No dosage adjustments are needed in patients with mild (creatinine clearance 50 to 80 mL/min) and moderate (creatinine clearance 30 to 50 mL/min) renal impairment (see **CLINICAL PHARMACOLOGY: Special Populations**).

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

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted August 20, 2004).

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999) and *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (February 2004). The guidances specify that labeling to be submitted in *pdf* format. To assist in our review, we request that labeling also be submitted in MS Word format. If formatted copies of all labeling pieces (i.e., package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper. For administrative purposes, these submissions should be designated "**FPL for approved supplement NDA 21-078/S-002**." Approval of this submission by FDA is not required before the labeling is used.

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.

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

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/s/

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Renata Albrecht

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