DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-078/S-012

GlaxoSmithKline
Attention: Debra Hackett
Director, US Regulatory Affairs
One Franklin Plaza
200 North 16th Street
FP1005
Philadelphia, PA 19102

Dear Ms. Hackett:

Please refer to your supplemental new drug application dated July 14, 2006, received July 17, 2006, 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 February 5, 2007, May 10, 2007, May 16, 2007, June 8, 2007, July 26, 2007, and August 30, 2007.

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

1. The following paragraph was added as the second paragraph under the **PRECAUTIONS/ General** subsection:

   Elevated liver function tests and rare cases of hepatitis have been reported with prophylactic use of MALARONE. A single case of hepatic failure requiring liver transplantation has also been reported with prophylactic use.

2. The following text was added as the fourth bullet under the **PRECAUTIONS/Information for Patients** subsection:

   - that rare serious adverse events such as hepatitis, severe skin reactions, neurological, and hematological events have been reported when MALARONE was used for the prophylaxis or treatment of malaria.

3. The following changes were made in the **ADVERSE REACTIONS/Post -Marketing Adverse Reactions** subsection:

   Post-Marketing Adverse Reactions: In addition to adverse events reported from clinical trials, the following events have been identified during world-wide post-approval use of

MALARONE. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to MALARONE.

~~***Skin/Hypersensitivity:*** Cutaneous~~ ***Blood and Lymphatic System Disorders:*** Neutropenia and rarely anemia. Pancytopenia in patients with severe renal impairment treated with proguanil.

Immune System Disorders: Allergic reactions ~~ranging from rash,photosensitivity,~~including angioedema, ~~and~~ urticaria ~~to~~, and rare cases of anaphylaxis~~, erythema multiforme, and Stevens-Johnson syndrome.~~

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

Hepatobiliary Disorders: Elevated liver function tests and rare cases of hepatitis; a single case of hepatic failure requiring transplant has been reported.

Skin and Subcutaneous Tissue Disorders: Photosensitivity, rash, and rare cases of erythema multiforme and Stevens-Johnson syndrome.

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 in the agreed upon labeling text dated August 30, 2007. Accordingly, this supplemental application is approved effective on the date of this letter.

If you have any questions, call Christine Lincoln, RN, M.S., MBA, Regulatory Health Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and Transplant Products
Office Antimicrobial Products
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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