DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-250/S-007, S-008

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

Dear Ms. Hackett:

Please refer to your supplemental new drug applications dated April 21, 1999 and December 17, 2001, received April 22, 1999 and December 19, 2001, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Halfan® (halofantrine hydrochloride) Tablets, 250 mg.

We acknowledge receipt of your submissions dated July 6, 2000, April 4, 2000 and January 2, 2002.

These "Changes Being Effected (CBE)" supplemental new drug applications provide for the following changes to the Halfan® package insert. Added text is noted by double underline:

1. WARNINGS
The following sentence was added and now appears after the second paragraph:

> "Caution should be used with concomitant intake of drugs which are known to significantly inhibit cytochrome $P_{450}IIIA_4$."

2. PRECAUTIONS
The following paragraph was added to the end of the **Drug Interactions** subsection:

> "*In vitro* studies have shown that drugs which inhibit cytochrome $CYPIIIA_4$, e.g., ketoconazole, lead to an inhibition of halofantrine metabolism. Further, in dogs orally administered ketoconazole, the metabolism of halofantrine was decreased (SEE WARNINGS)."

3. ADVERSE REACTIONS

The following paragraph was added to the **Postmarketing Experience** subsection as the second paragraph:

> **"**Hemolysis/hemolytic anemia (including immune hemolytic anemia) which may compromise renal function have been reported in patients with malaria who have been treated with halofantrine. Hemolytic reactions may also be observed in patients with malaria in the absence of halofantrine."

We have completed the review of these supplemental applications, 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 final printed labeling submitted on December 17, 2001. Accordingly, these supplemental applications are approved effective on the date of this letter.

At the next printing, please update the nomenclature for cytochrome P450 isozymes in **WARNINGS and PRECAUTIONS, Drug Interactions.** These labeling changes should be included in your next annual report:

> **WARNINGS**
> "Caution should be used with concomitant intake of drugs which are known to significantly inhibit ~~cytochrome P_{450}IIIA$_4$~~ the hepatic cytochrome P450 enzyme, CYP3A4."
>
> **PRECAUTIONS, Drug Interactions**
> "In vitro studies have shown that drugs which inhibit ~~cytochrome CYPIIIA$_4$~~ hepatic CYP3A4, e.g., ketoconazole, lead to an inhibition of halofantrine metabolism. Further, in dogs orally administered ketoconazole, the metabolism of halofantrine was decreased (SEE WARNINGS)."

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" 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.
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
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