DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20500/S-014

SUPPLEMENT APPROVAL

GlaxoSmithKline, LLC
Attention: Edward M. Yuhas, Ph.D.
Senior Director, Regulatory Affairs
1250 South Collegeville Road
Collegeville, PA 19426-0989

Dear Dr. Yuhas:

Please refer to your Supplemental New Drug Application (sNDA) dated February 24, 2012, received February 24, 2012, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mepron (atovaquone) 750 mg/5 mL, Suspension.

This "Prior Approval" supplemental new drug application provides for revising the organism *Pneumocystis carinii* to *Pneumocystis jiroveci* and other minor editorial revisions to the labeling.

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with the minor editorial revisions listed below and indicated in the enclosed labeling.

1. **Microbiology** section**, Activity In Vitro** and **Drug Resistance** subsections:

   Activity In Vitro: Several laboratories, using different in vitro methodologies, have shown the IC_{50} (50% inhibitory concentration) of atovaquone against rat *P.~~ carinii~~ jiroveci* to be in the range of 0.1 to 3.0 mcg/mL.

   Drug Resistance: Phenotypic resistance to atovaquone in vitro has not been demonstrated for *P. jiroveci*. However, in 2 patients who developed *Pneumocystis~~.~~ carinii* pneumonia (PCP) after prophylaxis with atovaquone, DNA sequence analysis identified mutations in the predicted amino acid sequence of *P. jiroveci* cytochrome b (a likely target site for atovaquone). The clinical significance of this is unknown.

2. **Clinical Pharmacology** section**, Relationship Between Plasma Atovaquone Concentration and Clinical Outcome** subsection:

   In a comparative study of atovaquone tablets with TMP-SMX for oral treatment of mild-to-moderate ~~*Pneumocystis carinii* pneumonia (PCP)~~ (see INDICATIONS AND USAGE), where AIDS patients received 750 mg atovaquone tablets 3 times daily for 21 days, the mean steady-state atovaquone concentration was 13.9 ± 6.9 mcg/mL

(n = 133). Analysis of these data established a relationship between plasma atovaquone concentration and successful treatment. This is shown in Table 2.

3. **PRECAUTIONS** section**, Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection:

   Carcinogenicity studies in rats were negative; 24-month studies in mice showed treatment-related increases in incidence of hepatocellular adenoma and hepatocellular carcinoma at all doses tested which ranged from 1.4 to 3.6 times the average steady-state plasma concentrations in humans during acute treatment of ~~*Pneumocystis carinii* pneumonia~~ PCP. Atovaquone was negative with or without metabolic activation in the Ames *Salmonella* mutagenicity assay, the Mouse Lymphoma mutagenesis assay, and the Cultured Human Lymphocyte cytogenetic assay. No evidence of genotoxicity was observed in the in vivo Mouse Micronucleus assay.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled, "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, M.D., M.P.H.
Deputy Director for Safety
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

SUMATHI NAMBIAR
03/01/2013