DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-666/S-004

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

Dear Ms. Hackett:

Please refer to your supplemental new drug application dated February 21, 2007, received February 22, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ALBENZA® (albendazole) Tablets, 200 mg.

We acknowledge receipt of your submission dated June 29 and August 6, 2007.

This "Changes Being Effected" supplemental new drug application provide for the following changes:

- **DESCRIPTION** section revised;
- **WARNINGS** section revised to include safety information regarding bone marrow suppression;
- **PRECAUTIONS**/**Information for Patients** subsection revised to include information in difficulties in swallowing the tablets whole, particularly young children;
- **PRECAUTIONS/Laboratory Tests/White Blood Cell Count** subsection revised to included safety information regarding bone marrow suppression;
- **PRECUATIONS/Laboratory Tests/Liver Function** subsection revised to include information regarding liver failure;
- **ADVERSE REACTIONS** section headings reformatted to the (MedDRA) SOC LIST internationally agreed order, revised to include information regarding bone marrow suppression, and addition of a post-marketing adverse reaction subsection;
- **DOSAGE AND ADMINISTRATION** section to include information for young children.

The proposed revisions to the package insert are listed below (<u>underlined</u> = added text, ~~strikethrough~~ = deleted text):

1. In the **DESCRIPTION** section, the third paragraph is revised as follows:

   Inactive ingredients consist of: carnauba wax, ~~hydroxypropyl methylcellulose~~ <u>hypromellose</u>, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, sodium lauryl sulfate, sodium saccharin, sodium starch glycolate, and starch.

2. In the **WARNINGS** section, the first paragraph reads as follows:

> Rare fatalities associated with the use of ALBENZA have been reported due to granulocytopenia or pancytopenia (see **PRECAUTIONS).** Albendazole has been shown to cause bone marrow suppression, aplastic anemia, and agranulocytosis in patients with and without underlying hepatic dysfunction. Blood counts should be monitored at the beginning of each 28-day cycle of therapy, and every 2 weeks while on therapy with albendazo1e in all patients. ~~Albendazole may be continued if the total white blood cell count and absolute neutrophil count decrease appear modest and do not progress.~~
> Patients with liver disease, including hepatic echinococcosis, appear to be more at risk for bone marrow suppression leading to pancytopenia, aplastic anemia, agranulocytosis, and leukopenia attributable to albendazole and warrant closer monitoring of blood counts. Albendazole should be discontinued in all patients if clinically significant decreases in blood cell counts occur.

3. In the **PRECAUTIONS/Information for Patients** subsection, a new bullet was added at the beginning of the section as follows:

> - Some people, particularly young children, may experience difficulties swallowing the tablets whole. In young children, the tablets should be crushed or chewed and swallowed with a drink of water.

4. In the **PRECAUTIONS/Laboratory Tests/White Blood Cell Count** subsection, the text was revised as follows:

> Albendazole has been shown to cause occasional (less than 1% of treated patients) reversible reductions in total white blood cell count. Rarely, more significant reductions may be encountered including granulocytopenia, agranulocytosis, or pancytopenia.Blood counts should be performed at the start of each 28-day treatment cycle and every 2 weeks during each 28-day cycle in all patients. Patients with liver disease, including hepatic echinococcosis, appear to be more at risk of bone marrow suppression and warrant closer monitoring of blood counts (see **WARNINGS**). ~~Albendazole may be continued if the total white blood cell count decrease appears modest and does not progress.~~ Albendazole should be discontinued in all patients if clinically significant decreases in blood cell counts occur.

5. In the **PRECAUTIONS/Laboratory Tests/Liver Function** subsection, the text was revised as follows:

> In clinical trials, treatment with albendazole has been associated with mild to moderate elevations of hepatic enzymes in approximately 16% of patients. These elevations have generally returned to normal upon discontinuation of therapy. There have also been case reports of acute liver failure of uncertain causality and hepatitis (see **ADVERSE REACTIONS**).
>
> Liver function tests (transaminases) should be performed before the start of each treatment cycle and at least every 2 weeks during treatment. If hepatic enzymes exceed twice the upper limit of normal, consideration should be given to discontinuing ~~are significantly increased~~ albendazole therapy based on individual patient circumstances~~, should be discontinued~~. Restarting albendazole treatment in patients whose hepatic enzymes have normalized off treatment is an individual decision that should take into account the risk/benefit of further

albendazole usage. ~~Therapy can be reinstituted when liver enzymes have returned to pretreatment levels, but~~ L~~l~~aboratory tests should be performed frequently if albendazole treatment is restarted ~~during repeat therapy~~.

Patients with abnormal liver function test results ~~prior to commencing albendazole therapy should be carefully evaluated, since the drug is metabolized by the liver and has been associated with hepatotoxicity in a few patients~~ are at increased risk for hepatotoxicity and bone marrow suppression (see **WARNINGS**). Therapy should be discontinued if liver enzymes are significantly increased or if clinically significant decreases in blood cell counts occur.

6. In the **ADVERSE REACTIONS** section**,** the third paragraph and on reads as follows:

The following adverse events were observed at an incidence of < 1%:

~~**Hematologic**~~ **Blood and Lymphatic System Disorders**: Leukopenia. There have been rare reports of granulocytopenia, pancytopenia, agranulocytosis, or thrombocytopenia (see **WARNINGS**). Patients with liver disease including hepatic echinococcosis, appear to be more at risk of bone marrow suppression (see **WARNINGS** and **PRECAUTIONS**).

~~**Dermatologic:**~~ **Immune System Disorders:** Hypersensitivity reactions, including ~~R~~rash and urticaria.

~~**Hypersensitivity**: allergic Reactions.~~

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 ALBENZA. 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 ALBENZA.

Blood and Lymphatic System Disorders: Aplastic anemia, bone marrow suppression, neutropenia.

Hepatobiliary Disorders: Elevations of hepatic enzymes, hepatitis, acute liver failure.

Skin and Subcutaneous Tissue Disorders: Erythema multiforme, Stevens-Johnson syndrome.

Renal and Urinary Disorders: Acute renal failure ~~----------~~

7. In the **DOSAGE AND ADMINISTRATION** section, the first paragraph reads as follows:

Dosing of ALBENZA will vary, depending upon which of the following parasitic infections is being treated. In young children, the tablets should be crushed or chewed and swallowed with a drink of water

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

Submit revised content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

Marketing the product with FPL that is not identical to the approved labeling text and in the required format may render the product misbranded and an unapproved new drug.

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

MedWatch
Food and Drug Administration
HFD-001, Suite 5100
5515 Security Lane
Rockville, MD 20852

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 Hyun Son, Pharm.D., Regulatory 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 of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Package Insert

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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