



NDA 08-578/S-016

GlaxoSmithKline
ATTN: David M. Cocchetto, Ph.D.
Vice President, Antiviral/Antibacterial Regulatory Affairs
P.O. Box 13398
Five Moore Drive
Research Triangle Park, NC 27709-3398

Dear Dr. Cocchetto:

Please refer to your supplemental new drug application dated May 21, 2003, received May 22, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DARAPRIM[®] (pyrimethamine) Tablets, 25 mg.

We acknowledge the receipt of your submission dated August 11, 2003.

This "Changes Being Effected" supplemental new drug application provides for the following changes to the DARAPRIM[®] package insert. Deleted text is noted by ~~striketrough~~ and added text is noted by double underline:

1. The following information was added to the **CONTRAINDICATIONS** section:

Use of DARAPRIM is contraindicated in patients with known hypersensitivity to pyrimethamine or to any component of the formulation. Use of the drug is also contraindicated in patients with documented megaloblastic anemia due to folate deficiency.

2. The following information was added and deleted in the **PRECAUTIONS, Drug Interactions** subsection:

Drug Interactions: Pyrimethamine may be used with sulfonamides, quinine and other antimalarials, and with other antibiotics. However, the concomitant use of other antifolate drugs, ~~such as or agents associated with myelosuppression including~~ sulfonamides or trimethoprim-sulfamethoxazole combinations, proguanil, zidovudine, or cytostatic agents (e.g., methotrexate), while the patient is receiving pyrimethamine, may increase the risk of bone marrow suppression. If signs of folate deficiency develop, pyrimethamine should be discontinued. Folinic acid (leucovorin) should be administered until normal hematopoiesis is restored (see WARNINGS). Mild hepatotoxicity has been reported in some patients when lorazepam and pyrimethamine were administered concomitantly.

3. The following information was added to the **PRECAUTIONS, Nursing Mothers** subsection:

Nursing Mothers: Pyrimethamine is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from pyrimethamine and from concurrent use of a sulfonamide with DARAPRIM for treatment of some patients with toxoplasmosis, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother (see WARNINGS and PRECAUTIONS: Pregnancy).

4. The following information was added to the **ADVERSE REACTIONS** section:

Hypersensitivity reactions, occasionally severe (such as Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, and anaphylaxis), and hyperphenylalaninemia, can occur particularly when pyrimethamine is administered concomitantly with a sulfonamide. Consult the complete prescribing information for the relevant sulfonamide for sulfonamide-associated adverse events. With doses of pyrimethamine used for the treatment of toxoplasmosis, anorexia and vomiting may occur. Vomiting may be minimized by giving the medication with meals; it usually disappears promptly upon reduction of dosage. Doses used in toxoplasmosis may produce megaloblastic anemia, leukopenia, thrombocytopenia, pancytopenia, atrophic glossitis, hematuria, and disorders of cardiac rhythm. Hematologic effects, however, may also occur at low doses in certain individuals (see PRECAUTIONS: General).

Pulmonary eosinophilia has been reported rarely.

We completed our review of this supplemental new drug application, as amended. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on May 21, 2003.

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 Christine Lincoln, RN, MS, MBA, 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

**This is a representation of an electronic record that was signed electronically and
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/s/

Renata Albrecht
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