DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

APR 23 1999

TRANSMITTED VIA FACSIMILE

Michele M. Hardy
Director, Advertising and Labeling Policy
Glaxo Wellcome Inc.
Five Moore Drive PO Box 13398
Research Triangle Park, North Carolina 27709

Re: NDA 20-857
Combivir Tablets
(lamivudine/zidovudine tablets)
Macmis # 7891

Dear Ms. Hardy:

The Division of Drug Marketing, Advertising, and Communications ("DDMAC") has reviewed materials in support of Combivir Tablets ("Combivir") that Glaxo Wellcome Inc. ("Glaxo") has submitted under cover of FDA Form 2253. Specifically, we refer to journal advertisements-CBV304R0 (two versions, eight sizes, submitted March 29, 1999), a magic sticker-CBV259R0 and promotional letter-CBV279R0 (submitted March 30, 1999).

Dissemination of these materials in promotion of Combivir violates the Federal Food, Drug and Cosmetic Act, and applicable regulations, because they are lacking in fair balance or otherwise misleading. Promotional materials must present side effects with a detail, readability and prominence that is reasonably comparable to the presentation of information relating to the effectiveness of the drug. The risk information that you have presented in the above referenced advertisements, promotional letter and magic sticker is lacking, incomplete, and/or not presented in a manner that is reasonably comparable in prominence and readability to your presentation of the benefits of Combivir.

In the advertisements and promotional letter, you have omitted important risk information that is prominently positioned in the boxed "Warning" of Combivir's package insert. Specifically, you have not disclosed that "zidovudine, one of the two active ingredients in Combivir, has been associated with hematologic toxicity including neutropenia and severe anemia, particularly in patients with advanced HIV," and that "[p]rolonged use of Zidovudine has been associated with symptomatic myopathy." In your presentation of risks, you do not attribute the potentially fatal side effects of lactic acidosis and severe hepatomegaly with steatosis to nucleoside analogues, such as Combivir (lamivudine and zidovudine). Instead, you state that these side effects "have been reported rarely with

some HIV drugs," or "have been reported with the use of antiretroviral nucleoside analogues." This presentation minimizes the significance of these risks (reported with both zidovudine and lamivudine) for patients taking Combivir. Moreover, you have presented these risks in a type-size and layout that minimizes their readability and importance. In comparison, you have presented benefits of Combivir in large, bright, colorful, bold, contrasting print, and short easy-to-read sentences.

In addition, on the magic sticker you make reference to the indication for Combivir, for example, "www.treathiv.com." However, you fail to disclose any risks or safety information that are associated with the use of Combivir.

Glaxo should immediately cease dissemination of these and other similar promotional materials for Combivir that contain the same or similar presentations. You should submit to us, by May 7, 1999, a written response that includes a list of materials that contain these or similar presentations, and describe your intent and plans to immediately cease use of these materials, including the date of discontinuation.

Please direct your response to the undersigned by facsimile at (301) 594-6771, or by mail at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-40, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. In all future correspondence regarding this matter, please refer to MACMIS # 7891 and the NDA number. As a reminder, only written communications are considered official.

Sincerely,

Sherrie Shade, R.Ph., J.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications