NDA 19-655/SLR-032
NDA 19-910/SLR-021
NDA 20-518/SLR-004

GlaxoSmithKline
Attention: Martha Anne A. Moore, RPh
Product Director, Regulatory Affairs
Five Moore Drive
Research Triangle Park, NC 27709

30 MAR 2001

Dear Ms. Moore:

Please refer to your supplemental new drug applications dated March 9, 1998, received March 10, 1999, submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act for RETROVIR® (zidovudine) Capsules, RETROVIR® (zidovudine) Syrup, RETROVIR® (zidovudine) Tablets.

We acknowledge receipt of your submissions dated March 9, 1998, April 27, 1998, April 15, 1999, September 18, 2000, and November 17, 2000. Your submission of November 17, 2000 constituted a complete response to our March 4, 1998 action letter.

These supplemental new drug applications provide for changes in the following sections of the final printed labeling:

(1) Black Box Warning is updated to conform to labeling of other antiretroviral drugs.

(2) Microbiology section is not updated in this supplement but is deferred to a later submission.

(3) Clinical Pharmacology section is updated to reflect the current therapeutic practice. Drug Interactions section is presented in tabular rather than text form for ease of understanding and to be consistent with other classes of drugs and antiretrovirals.

(4) Indications and Usage section concisely summarizes the history and multiple clinical studies conducted during the post-marketing phase in a more understandable format. The Dose-Frequency Study section is deleted because comparison of doses is no longer necessary in order to provide details about the change from the original dosing schedule to those used today.

(5) Warnings section is updated to include information about lactic acidosis/severe hepatomegaly with steatosis to be consistent with labeling for nucleoside analogs and other antiretroviral agents

(6) Precautions section is updated to be consistent with the labeling of other antiretroviral agents.

(7) Adverse Reactions section is updated to reflect and highlight the safety of RETROVIR at doses similar to that of currently used doses. This is done in study 019 that compared RETROVIR 500mg/day to placebo. Also, the pediatric study ACTG300 was retained that compared EPIVIR plus RETROVIR with didanosine.

(8) Dosage and Administration section is updated to delete the reference to the dose of 500mg daily (100mg five times daily) to reflect current dosing schedules of 600mg daily in divided doses in combination with other antiretroviral agents for adults. However, the wording under the Maternal-Fetal HIV Transmission section retains the recommendation for a dose of 100mg five times daily for maternal dosing.

This section is also modified to suggest a dose reduction may be needed in certain situations, but no specific dosing recommendations are made.

In addition to the changes referenced above, please make the following minor changes in the November 17, 2000 labeling attached to this letter:

(1) Page 5, Lines 122 –123, the word "is" is deleted and the word "are" is inserted. The sentence in the final printed labeling is as follows:

"Overall, zidovudine pharmacokinetics in pediatric patients greater than 3 months of age **are** similar to those in adult patients."

(2) Page 8, Line 198, the letter "t" is inserted into the word "treatment-naïve." The sentence in the final printed labeling is as follows:

"In controlled studies of **treatment-naive** patients conducted between 1986 and 1989, monotherapy with RETROVIR, as compared to placebo, reduced the risk of HIV disease progression, as assessed using endpoints that included the occurrence of HIV-related illnesses, AIDS-defining events, or death."

(3) Page 9, Line 233, the following sentence is inserted immediately after Warnings: in the final printed labeling:

"COMBIVIR is a combination tablet of zidovudine and lamivudine. RETROVIR should not be administered concomitantly with COMBIVIR."

(4) Page 13, Line 382, the word "have" is deleted and the word "had" is inserted. Line 382, the word "are" is deleted and the word "were" is inserted. Line 383, a period is inserted immediately following the word "immunosuppression." The sentence in the final printed labeling is as follows:

"RETROVIR has been studied in HIV-infected pediatric patients over 3 months of age who **had** HIV-related symptoms or who **were** asymptomatic with abnormal laboratory values indicating significant HIV-related immunosuppression**."**

(5) Page 19, Lines 529 535, Copyright and Date of Issue Information section, the former corporate name of "Glaxo Wellcome" is deleted and the new corporate name "**GlaxoSmithKline**" is inserted. Also, the current copyright date is inserted in this section.

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 products are safe and effective for use as recommended in the agreed upon labeling text. Accordingly, these supplemental applications, with the minor changes listed above, are approved effective on the date of this letter.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavyweight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 19-655/SLR-032, 19-910/SLR-021, 19-518/SLR-004." Approval of these submissions by FDA is not required before the labeling is used. However, marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

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:

NDA 19-655
NDA 19-910
NDA 20-518

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 Marsha S. Holloman, BS Pharm, JD, Regulatory Project Manager, at (301) 827-2335.

Sincerely,

Debra B. Birnkrant, MD
Acting Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research