DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 19655/S-052
NDA 19910/S-039
NDA 20518/S-022

SUPPLEMENT APPROVAL

GlaxoSmithKline
Attention: Laura Bacot, US Regulatory Regional Representative
Global Regulatory Affairs
PO Box 133398
5 Moore Drive, Room 5.5218,
Research Triangle Park, NC 27709-3398

Dear Ms. Bacot:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received October 14, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Retrovir ® (zidovudine) Capsules (NDA 19655), Syrup (NDA 19910), and Tablets (NDA 20518).

We also refer to our letter dated September 15, 2011, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for antiretroviral products. This information pertains to the risk of the autoimmune disorder as syndromes that can occur in the setting of immune reconstitution with the use of antiretroviral products.

In addition, we refer to non-safety labeling changes in our September 15, 2011 letter for all antiretroviral products based on recent studies demonstrating decreased transmission of HIV when HIV-infected patients or their uninfected partners take antiretroviral medication.

These supplemental new drug applications provide for revisions to the labeling for Retrovir ® (zidovudine) Capsules, Syrup, and Tablets, consistent with our September 15, 2011, letter as follows (additions are noted by underline and deletion are noted by ~~strikethrough~~).

1. The phrase, "Warnings and Precautions, Immune Reconstitution ------- (month year) Syndrome (5.6)" has been added under the **RECENT MAJOR CHANGES** in the Highlights section.

2. The revision date has been changed from 01/2011 to mo/yr at the end of the **HIGHLIGHTS** section and the last page of the labeling.

3. The first and the fourth bulleted sentences of the **DOSAGE AND ADMINISTRATION** section in the **HIGHLIGHTS** section has been revised as follows, respectively:

- Treatment of HIV-1 infection:
  Adults: 600 mg/day in divided doses with other antiretroviral agents.
  Pediatric patients (aged 4 weeks to <18 years ~~of age~~): Dosage should be calculated based on body weight not to exceed adult dose. (2.1)
- Renal I~~i~~mpairment: Recommended dosage in hemodialysis or peritoneal dialysis patients is 100 mg every 6 to 8 hours. (2.4)

4. The **WARNINGS AND PRECAUTIONS** section has been revised in the Highlights section to be consistent with TRIZIVIR and EPZICOM and to meet ½ page requirement as follows:

- See boxed warning for information about the following: hematologic toxicity, myopathy, and lactic acidosis and severe hepatomegaly. (5.1, 5.2, 5.3)
- ~~Hematologic toxicity/bone marrow suppression including neutropenia and severe anemia have been associated with the use of zidovudine. (5.1)~~
- ~~Symptomatic myopathy associated with prolonged use of zidovudine. (5.2)~~
- ~~Lactic acidosis and hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues including RETROVIR. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. (5.3)~~
- Exacerbation of anemia has been reported in HIV-1/HCV co-infected patients receiving ribavirin and zidovudine. Coadministration of ribavirin and zidovudine is not advised. (5.4)
- Hepatic decompensation, (some fatal), has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy and interferon alfa with/without ribavirin. Discontinue zidovudine as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.4)
- RETROVIR should not be administered with other zidovudine-containing combination products. (5.5)
- Immune reconstitution syndrome (5.6) and redistribution/accumulation of body fat (5.7) have been reported in patients treated with combination antiretroviral therapy.

5. The subheadings were added in the Boxed Warning in the **FULL PRECRIBING INFORMATION** section for consistency with TRIZIVIR and EPZICOM as follows:

WARNING: RISK OF HEMATOLOGIC TOXICITY, MYOPATHY, LACTIC ACIDOSIS
Hematologic Toxicity: RETROVIR® (zidovudine) Tablets, Capsules, and Syrup have been associated with hematologic toxicity including neutropenia and severe anemia, particularly in patients with advanced HIV-1 disease *[see Warnings and Precautions (5.1)]*.
Myopathy: Prolonged use of RETROVIR has been associated with symptomatic myopathy *[see Warnings and Precautions (5.2)]*.
Lactic Acidosis and Severe Hepatomegaly: Lactic acidosis and severe hepatomegaly

with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including RETROVIR and other antiretrovirals. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur *[see Warnings and Precautions (5.3)]*.

6. The **DOSAGE AND ADMINISTRATION/Treatment of HIV-1 Infection** sub-section:

   a. The title of the second paragraph has been revised as follows:
      Pediatric Patients ~~(~~Aged 4 Weeks to <18 Years ~~of Age)~~:
   b. The first row in Table 1 has been revised as follows:

Body Weight (kg)	Total Daily Dose	Dosage Regimen and Dose	
		~~b.i.d.~~Twice Daily	~~t.i.d.~~Three Times Daily

7. The **WARNINGS AND PRECAUTIONS/Immune Reconstitution Syndrome** sub-section has been revised as follows:

   Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including RETROVIR. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

   Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution, however, the time to onset is more variable, and can occur many months after initiation of treatment.

8. The **ADVERSE REACTIONS** section: The position of the title, **6.1 Clinical Trials Experience**, has been moved from the first line of the section to be placed after the last bullet of the first paragraph.

9. In the **CLINICAL PHARMACOLOGY/Pharmacokinetics** sub-section, a dash has been added between "one fifth" in the fifth sentence of the Metabolism and Elimination titled paragraph and reads as "one-fifth".

10. The **CLINICAL PHARMACOLOGY/Pediatric Patients** sub-section:

    a. The title of the first paragraph has been revised as follows:
       Patients Aged 3 Months to 12 Years ~~of Age~~:
    b. The title of the second paragraph has been revised as follows:
       Patients Aged ~~<~~ Less Than 3 Months ~~of Age~~:

    c. The first row in Table 8 has been revised as follows:

Parameter	Birth to 14 Days ~~of Age~~	Aged 14 Days to 3 Months ~~of Age~~	Aged 3 Months to 12 Years ~~of Age~~

11. In the **NONCLINICAL TOXICOLOGY/Reproductive and Developmental Toxicology Studies** sub-section, a dash has been added between "one half" and "one sixth" in the third sentence of the first paragraph and reads as "one-half" and "one-sixth".

12. The abbreviated word, "t.i.d" in the **CLINICAL STUDIES/Adults/**the second paragraph of the **Combination Therapy** sub-section was revised to three times daily.

13. The **PATIENT COUNSELING INFORMATION** section has been revised as follows:

The title of Section 17.1 was changed to **Advice for the Patient.**

The following paragraph was added underneath of the HIV-1/HCV Co-Infection sub-section:

Use With Other Zidovudine-Containing Products: RETROVIR should not be administered with combination products that contain zidovudine as one of their components (e.g., COMBIVIR [lamivudine and zidovudine] Tablets or TRIZIVIR [abacavir sulfate, lamivudine, and zidovudine] Tablets) *[see Warnings and Precautions (5.5)]*.

Information About ~~Therapy with COMBIVIR~~HIV-1 Infection: RETROVIR is not a cure for HIV-1 infection, and patients may continue to ~~acquire~~ experience illnesses associated with HIV-1 infection, including opportunistic infections. ~~Therefore, p~~Patients should remain under the care of a physician when using RETROVIR.~~be informed advised to seek medical care for any significant change in their health status.~~
Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** ~~We do not know if RETROVIR can be passed to your baby in your breast milk and whether it could harm your baby. Also, m~~Zidovudine is excreted in human breast milk. Mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

Patients should be informed to take all HIV medications exactly as prescribed. ~~Patients should be informed of the importance of taking RETROVIR exactly as prescribed. They should be informed not to share medication and not to exceed the recommended dose. Patients should be informed that the long-term effects of RETROVIR are unknown at this time.~~

~~Patients should be informed that therapy with RETROVIR has not been shown to reduce the risk of transmission of HIV-1 to others through sexual contact or blood contamination.~~

We have completed our review of these supplemental applications. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

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, Medication Guide), 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).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html;

instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

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 Kyong Hyon, Safety Regulatory Project Manager, at (301) 796-0734.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Deputy Director for Safety
Division of Antiviral Products
Office Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
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/

KENDALL A MARCUS
11/18/2011