DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20857/S-028

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 Application (sNDA) dated and received October 13, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Combivir® (lamivudine/zidovudine) Tablets, 150 mg/300 mg.

We acknowledge receipt of your amendment dated November 1, 2011.

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.

This supplemental new drug application and an amendment provide for revisions to the labeling for Combivir® (lamivudine/zidovudine) Tablets, 150 mg/300 mg, consistent with our September 15, 2011 letter and inclusion of Complera in the list of drugs that should not be administered with lamivudine-containing products, as follows (additions are noted by underline and deletion are noted by ~~strikethrough)~~.

1. The fourth bullet of the Boxed Warning in the **HIGHLIGHTS** section of the labeling has been reformatted for consistency with TRIZIVIR and EPZICOM as follows:

   Severe, ~~A~~acute exacerbations of hepatitis B have been reported in patients who are coinfected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine, a component of COMBIVIR. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.4)

2. The phrase, "Warnings and Precautions, Immune Reconstitution Syndrome (5.8) ---------- (month/year)" has been added under the **RECENT MAJOR CHANGES** in the Highlights section of the labeling.

3. 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, symptomatic myopathy, lactic acidosis and severe hepatomegaly, and severe acute exacerbations of hepatitis B. (5.1, 5.2, 5.3. 5.4)
   - ~~Hematologic toxicity/bone marrow suppression including neutropenia and anemia have been associated with the use of zidovudine, one of the components of COMBIVIR. (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 zidovudine. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur. (5.3)~~
   - ~~Acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV-1) and have discontinued lamivudine, a component of COMBIVIR. Monitor hepatic function closely in these patients and, if appropriate, initiate anti-hepatitis B treatment. (5.4)~~
   - COMBIVIR should not be administered with other lamivudine- or zidovudine-containing products or emtricitabine-containing products. (5.5)
   - Hepatic decompensation, some fatal, has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy and interferon alfa with/without ribavirin. Discontinue COMBIVIR as medically appropriate and consider dose reduction or discontinuation of interferon alfa, ribavirin, or both. (5.6)
   - Exacerbation of anemia has been reported in HIV-1/HCV co-infected patients receiving ribavirin and zidovudine. Co-administration of ribavirin and zidovudine is not advised. (5.6)
   - Pancreatitis: Use with caution in pediatric patients with a history of pancreatitis or other significant risk factors for pancreatitis. Discontinue treatment as clinically appropriate. (5.7)
   - Immune reconstitution syndrome (5.8) and redistribution/accumulation of body fat (5.9) have been reported in patients treated with combination antiretroviral therapy.

4. The revision date has been changed from September 2010 to mo/yr throughout the label.

5. The Boxed Warning in the **FULL PRECRIBING INFORMATION** section has been reformatted for consistency with TRIZIVIR and EPZICOM as follows:

> **WARNING: HEMATOLOGIC TOXICITY, MYOPATHY, LACTIC ACIDOSIS, EXACERBATIONS OF HEPATITIS B**
> **Hematologic Toxicity: Zidovudine, one of the 2 active ingredients in COMBIVIR® (lamivudine and zidovudine) Tablets, has been associated with hematologic toxicity including neutropenia and anemia, particularly in patients with advanced HIV-1 disease *[see Warnings and Precautions (5.1)]*.**
> **Myopathy: Prolonged use of zidovudine has been associated with symptomatic myopathy *[see Warnings and Precautions (5.2)]*.**
> **Lactic Acidosis and Severe Hepatomegaly: Lactic acidosis and hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including lamivudine, zidovudine, and other antiretrovirals. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur *[see Warnings and Precautions (5.3)]*.**
> **Exacerbations of Hepatitis B: Severe, ~~A~~acute exacerbations of hepatitis B have been reported in patients who are co-infected with hepatitis B virus (HBV) and HIV-1 and have discontinued lamivudine, which is one component of COMBIVIR. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue COMBIVIR and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.4)]*.**

6. The **DOSAGE FORMS AND STRENGTHS** section has been updated for consistency with TRIZIVIR and EPZICOM and to include the strengths of the active ingredients as follows:

   COMBIVIR Tablets contain 150 mg of lamivudine and 300 mg of zidovudine. The tablets are white, scored, film-coated, modified capsule-shaped tablets, debossed on both tablet faces, such that when broken in half, the full "GX FC3" code is present on both halves of the tablet ("GX" on one face and "FC3" on the opposite face of the tablet).

7. The **WARNINGS AND PRECAUTIONS**/ Use With Other, Lamivudine-, Zidovudine-, and/or Emtricitabine-Containing Products sub-section has been revised as follows:

   COMBIVIR is a fixed-dose combination of lamivudine and zidovudine. COMBIVIR should not be administered concomitantly with other lamivudine- or zidovudine-containing products including EPIVIR® (lamivudine) Tablets and Oral Solution, EPIVIR-HBV Tablets and Oral Solution, RETROVIR® (zidovudine) Tablets, Capsules, Syrup, and IV Infusion, EPZICOM® (abacavir sulfate and lamivudine) Tablets, or TRIZIVIR® (abacavir sulfate, lamivudine, and zidovudine) Tablets; or emtricitabine-containing products, including ATRIPLA® (efavirenz, emtricitabine, and tenofovir), EMTRIVA® (emtricitabine), TRUVADA® (emtricitabine and tenofovir) or COMPLERA™ (rilpivirine/emtricitabine/tenofovir).

8. 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 COMBIVIR. 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.

9. A dash has been added between "one fifth" in the last sentence in the Zidovudine titled paragraph in the **CLINICAL PHARMACOLOGY/Pharmacokinetcs** sub-section and reads as "one-fifth".

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

11. The **PATIENT COUNSELING INFORMATION** section has been revised as follows to be consistent with RETROVIR:

Advice for the Patient

Neutropenia and Anemia: Patients should be informed that the important toxicities associated with zidovudine are neutropenia and/or anemia. They should be told of the extreme importance of having their blood counts followed closely while on therapy, especially for patients with advanced HIV-1 disease *[see Boxed Warning, Warnings and Precautions (5.1)]*.

Myopathy: Patients should be informed that myopathy and myositis with pathological changes, similar to that produced by HIV-1 disease, have been associated with prolonged use of zidovudine *[see Boxed Warning, Warnings and Precautions (5.2)]*.

Lactic Acidosis/Hepatomegaly: Patients should be informed that some HIV medicines, including COMBIVIR, can cause a rare, but serious condition called lactic acidosis with liver enlargement (hepatomegaly) *[see Boxed Warning, Warnings and Precautions (5.3)]*.

~~Co-infection With~~ HIV-1~~and~~/HBV Co-infection: Patients co-infected with HIV-1 and HBV should be informed that deterioration of liver disease has occurred in some cases when treatment with lamivudine was discontinued. Patients should be advised to discuss any changes in regimen with their physician *[see Warnings and Precautions (5.4)]*.

Use With Other Lamivudine-, Zidovudine-, and/or Emtricitabine-Containing Products: COMBIVIR should not be coadministered with drugs containing lamivudine, zidovudine, or emtricitabine, including EPIVIR (lamivudine), EPIVIR-HBV (lamivudine), RETROVIR (zidovudine), EPZICOM (abacavir sulfate and lamivudine), TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine), ATRIPLA (efavirenz, emtricitabine, and

tenofovir), EMTRIVA (emtricitabine), or TRUVADA (emtricitabine and tenofovir), or COMPLERA™ (rilpivirine/emtricitabine/tenofovir) *[see Warnings and Precautions (5.5)]*.

HIV-1/HCV Co-Infection: Patients with HIV-1/HCV co-infection should be informed that hepatic decompensation (some fatal) has occurred in HIV-1/HCV co-infected patients receiving combination antiretroviral therapy for HIV-1 and interferon alfa with or without ribavirin *[see Warnings and Precautions (5.6)]*.

Drug Interactions: Patients should be cautioned about the use of other medications, including ganciclovir, interferon alfa, and ribavirin, which may exacerbate the toxicity of zidovudine *[see Drug Interactions (7.3)]*.

Redistribution/Accumulation of Body Fat: Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long-term health effects of these conditions are not known at this time *[see Warnings and Precautions (5.9)]*.

12. The following section of the **PATIENT COUNSELING INFORMATION/ Advice for the Patient** sub-section has been revised to be consistent with TRIZIVIR, ZIAGEN, and EPZICOM and to meet FDA's non-safety labeling change recommendations as follows:

Information About ~~Therapy with COMBIVIR~~HIV-1 Infection: COMBIVIR is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using COMBIVIR. ~~Patients should be advised that the use of COMBIVIR has not been shown to reduce the risk of transmission of HIV-1 to others through sexual contact or blood contamination.~~

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 COMBIVIR can be passed to your baby in your breast milk and whether it could harm your baby. Also,~~ Lamivudine and zidovudine are excreted in human breast milk. ~~m~~Mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

~~Patients should be advised of the importance of taking COMBIVIR exactly as it is prescribed.~~ Patients should be informed to take all HIV medications exactly as prescribed.

~~COMBIVIR should not be coadministered with drugs containing lamivudine, zidovudine, or emtricitabine, including EPIVIR (lamivudine), EPIVIR-HBV (lamivudine), RETROVIR (zidovudine), EPZICOM (abacavir sulfate and lamivudine), TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine), ATRIPLA (efavirenz, emtricitabine, and tenofovir), EMTRIVA (emtricitabine), or TRUVADA (emtricitabine and tenofovir) *[see Warnings and Precautions (5.5)]*.~~

We have completed our review of this supplemental application, as amended. It is 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