DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20564/S-031
NDA 20596/S-030

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 Epivir® (lamivudine) Tablets (NDA 20564) and Oral Solution (NDA 20596).

We acknowledge receipt of your amendments 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.

These supplemental new drug applications and amendments provide for revisions to the labeling for Epivir® (lamivudine) Tablets and Oral Solution, 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 phrase, “Warnings and Precautions, Immune Reconstitution --------- (month/year)” Syndrome (5.6) has been added under the **RECENT MAJOR CHANGES** in the Highlights section of the labeling.

2. The revision date has been changed from September 2010 to mo/yr at the end of the **HIGHLIGHTS** section and the last page of the label.

3. The Boxed Warning in the **FULL PRECRIBING INFORMATION** section has been revised for consistency with TRIZIVIR and EPZICOM by adding subheadings as follows:

WARNING: RISK OF LACTIC ACIDOSIS, EXACERBATIONS OF HEPATITIS B IN CO-INFECTED PATIENTS UPON DISCONTINUATION OF EPIVIR®, DIFFERENT FORMULATIONS OF EPIVIR.

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 lamivudine and other antiretrovirals. Suspend treatment if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity occur *[see Warnings and Precautions (5.1)]*.

Exacerbations of Hepatitis B: Severe 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 EPIVIR. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months in patients who discontinue EPIVIR and are co-infected with HIV-1 and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted *[see Warnings and Precautions (5.2)]*.

Important Differences Among Lamivudine-Containing Products: EPIVIR Tablets and Oral Solution (used to treat HIV-1 infection) contain a higher dose of the active ingredient (lamivudine) than EPIVIR-HBV® Tablets and Oral Solution (used to treat chronic HBV infection). Patients with HIV-1 infection should receive only dosage forms appropriate for treatment of HIV-1 *[see Warnings and Precautions (5.2)]*.

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

EPIVIR should not be administered concomitantly with other lamivudine-containing products including EPIVIR-HBV Tablets, EPIVIR Oral Solution, COMBIVIR (lamivudine/zidovudine) Tablets, EPZICOM (abacavir sulfate and lamivudine) Tablets, or TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine) or emtricitabine-containing products, including ATRIPLA® (efavirenz, emtricitabine, and tenofovir), EMTRIVA® (emtricitabine), TRUVADA® (emtricitabine and tenofovir), or COMPLERA™ (rilpivirine/emtricitabine/tenofovir).

5. 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 EPIVIR. During the initial phase of combination antiretroviral treatment, patients whose immune system responds 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.

6. **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.

7. The **PATIENT COUNSELING INFORMATION** section has been revised to be consistent with Retrovir, Trizivir, Ziagen, and Epzicom by revising headings and rearranging the text throughout this section as follows :

Advice for the Patient

Lactic Acidosis/Hepatomegaly: Patients should be informed that some HIV medicines, including EPIVIR, can cause a rare, but serious condition called lactic acidosis with liver enlargement (hepatomegaly) *[see Boxed Warning, Warnings and Precautions (5.1)]*.

~~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 (5.2)]*.

Differences in Formulations of EPIVIR: Patients should be advised that EPIVIR Tablets and Oral Solution contain a higher dose of the same active ingredient (lamivudine) as EPIVIR-HBV Tablets and Oral Solution. If a decision is made to include lamivudine in the HIV-1 treatment regimen of a patient co-infected with HIV-1 and HBV, the formulation and dosage of lamivudine in EPIVIR (not EPIVIR-HBV) should be used *[see Warnings and Precautions (5.2)]*.

Use With Other Lamivudine- and Emtricitabine-Containing Products: EPIVIR should not be coadministered with drugs containing lamivudine or emtricitabine, including COMBIVIR (lamivudine/zidovudine) Tablets, EPZICOM (abacavir sulfate and lamivudine) Tablets, 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 (5.3)]*.

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 (5.4)]*.

Risk of Pancreatitis: Parents or guardians should be advised to monitor pediatric patients for signs and symptoms of pancreatitis *[see Warnings and Precautions (5.5)]*.

Redistribution/Accumulation of Body Fat: Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, including EPIVIR, and that the cause and long-term health effects of these conditions are not known at this time *[see Warnings and Precautions (5.7)]*.

Sucrose Content of EPIVIR Oral Solution: Diabetic patients should be advised that each 15-mL dose of EPIVIR Oral Solution contains 3 grams of sucrose *[see Description (11)]*.

Information About ~~Therapy With EPIVIR~~HIV-1 Infection EPIVIR 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 EPIVIR. ~~Patients should be advised that the use of EPIVIR 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 EPIVIR can be passed to your baby in your breast milk and whether it could harm your baby. Also,~~ Lamivudine is 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 that the long-term effects of EPIVIR are unknown at this time.~~

Patients should be informed to take all HIV medications exactly as prescribed.~~advised of the importance of taking EPIVIR with combination therapy on a regular dosing schedule and to avoid missing doses~~.

~~EPIVIR should not be coadministered with drugs containing lamivudine or emtricitabine, including COMBIVIR (lamivudine/zidovudine) Tablets, EPZICOM (abacavir sulfate and lamivudine) Tablets, TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine), ATRIPLA (efavirenz, emtricitabine, and tenofovir), EMTRIVA (emtricitabine) or TRUVADA (emtricitabine and tenofovir) *[see Warnings and Precautions (5.3)]*.~~

~~Redistribution/Accumulation of Body Fat: Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, including EPIVIR, and that the cause and long-term health effects of these conditions are not known at this time *[see Warnings and Precautions (5.7)]*.~~

~~Differences in Formulations of EPIVIR: Patients should be advised that EPIVIR Tablets and Oral Solution contain a higher dose of the same active ingredient (lamivudine) as EPIVIR-HBV Tablets and Oral Solution. If a decision is made to include lamivudine in the HIV-1 treatment regimen of a patient co-infected with HIV-1 and HBV, the formulation and dosage of lamivudine in EPIVIR (not EPIVIR-HBV) should be used *[see Warnings and Precautions (5.2)]*.~~

~~Co-infection With HIV-1 and HBV: 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 (5.2)]*.~~

~~Risk of Pancreatitis: Parents or guardians should be advised to monitor pediatric patients for signs and symptoms of pancreatitis *[see Warnings and Precautions (5.5)]*.~~

~~Sucrose Content of EPIVIR Oral Solution: Diabetic patients should be advised that each 15-mL dose of EPIVIR Oral Solution contains 3 grams of sucrose *[see Description (11)]*.~~

We have completed our review of these supplemental applications, as amended. 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/

KYONG M HYON
11/18/2011

KENDALL A MARCUS
11/18/2011