



NDA 21652/S-014

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 14, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Epzicom[®] (abacavir sulfate and lamivudine) Tablets.

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 Epzicom[®] (abacavir sulfate and lamivudine) Tablets, 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 ~~striketrough~~).

1. The **RECENT MAJOR CHANGES** in the Highlights section of the label has been added as follows:

-----**RECENT MAJOR CHANGES**-----
Warnings and Precautions, Immune Reconstitution Syndrome (5.5) -----(month
year)

2. The revision date has been changed from February 2011 to mo/yr at the end of the

HIGHLIGHTS section and the last page of the label.

3. 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 EPZICOM. 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.

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

EPZICOM contains fixed doses of 2 nucleoside analogues, abacavir and lamivudine, and should not be administered concomitantly with other abacavir-containing and/or lamivudine-containing products (ZIAGEN, EPIVIR, COMBIVIR® [lamivudine and zidovudine] Tablets, or TRIZIVIR® [abacavir sulfate, lamivudine, and zidovudine] Tablets); or emtricitabine-containing products, including ATRIPLA® (efavirenz, emtricitabine, and tenofovir disoproxil fumarate) Tablets, EMTRIVA® (emtricitabine) Capsules and Oral Solution, or TRUVADA® (emtricitabine and tenofovir disoproxil fumarate) Tablets, or COMPLERA™ (rilpivirine/emtricitabine/tenofovir).

5. The title of the **PATIENT COUNSELING INFORMATION** section has been revised as follows:

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

~~See Medication Guide.~~

6. The last bulleted sentence of the **PATIENT COUNSELING INFORMATION/Hypersensitivity Reaction** sub-section has been revised as follows:

- EPZICOM should not be administered concomitantly with ATRIPLA, COMBIVIR, COMPLERA, EMTRIVA, EPIVIR, EPIVIR-HBV, TRIZIVIR, TRUVADA, or ZIAGEN.

7. Several sub-sections of the **PATIENT COUNSELING INFORMATION** section have been revised to be consistent with Combivir, Epivir, and Retrovir as follows:

Lactic Acidosis/Hepatomegaly: Inform patients that some HIV medicines, including EPZICOM, can cause a rare, but serious condition called lactic acidosis with liver enlargement (hepatomegaly) [*see Boxed Warning, Warnings and Precautions (5.2)*].

~~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 (5.23)*].

~~HIV-1/HCV Co-Infection:~~ Patients co-infected 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)*].

~~Redistribution/Accumulation of Body Fat:~~ Inform patients 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 (5.6)*].

8. The **PATIENT COUNSELING INFORMATION/Information About HIV-1 Infection** sub-section has been revised as follows:

EPZICOM 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 EPZICOM. ~~Advise patients that the use of EPZICOM has not been shown to reduce the risk of transmission of HIV-1 to others through sexual contact or blood contamination.~~

~~Patients should be informed~~ advise to take all HIV medications exactly as prescribed ~~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 EPZICOM can be passed to your baby in your breast milk and whether it could harm your baby.~~ Lamivudine is excreted in human breast milk. It is not known if abacavir can be passed to your baby in your breast milk and whether it could harm your baby. Also, 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.

9. The **PATIENT COUNSELING INFORMATION/Importance of Taking EPZICOM as Prescribed** sub-section has been revised as follows for consistency with TRIZIVIR and EPZICOM:

~~Importance of Taking EPZICOM as Prescribed:~~ Inform patients to take EPZICOM on a regular dosing schedule and to avoid missing doses. EPZICOM Tablets are for oral ingestion only.

10. MEDICATION GUIDE

- a. The last bulleted paragraph in the section “**Before you take EPZICOM tell your healthcare provider if you:**” has been revised as follows:

- **are breastfeeding or plan to breastfeed.** ~~EPZICOM can pass into your breast milk. You should not breastfeed if you are taking EPZICOM. If you are a woman who has or will have a baby while taking EPZICOM, talk to your healthcare provider about the best way to feed your baby. The Center for Disease Control and Prevention (CDC) recommend that HIV-infected mothers **not** breastfeed to avoid the risk of passing HIV infection to your baby. **Do not breastfeed.** Lamivudine is excreted in human breast milk. We do not know if EPZICOM/abacavir can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.~~

- b. The bulleted list in the “**Especially tell your healthcare provider if you take:**” section has been revised as follows:

- alcohol
- medicines used to treat hepatitis viruses such as interferon or ribavirin.
- methadone
- ATRIPLA® (efavirenz, emtricitabine, and tenofovir)
- COMBIVIR® (lamivudine and zidovudine)
- COMPLERA™ (rilpivirine/emtricitabine/tenofovir)
- EMTRIVA® (emtricitabine)
- EPIVIR or EPIVIR-HBV® (lamivudine, 3TC)
- TRIZIVIR (abacavir sulfate, lamivudine, and zidovudine)
- TRUVADA® (emtricitabine and tenofovir)
- ZIAGEN (abacavir sulfate)

- c. The paragraph after the fourth bullet in the “**How Should I take EPZICOM?**” sub-section has been revised as follows:

If you stop your anti-HIV ~~drugs~~ medicines, even for a short time, the amount of virus in your blood may increase and the virus may become harder to treat. If you take too much EPZICOM, call your healthcare provider or poison control center or go to the nearest hospital emergency room right away.

- d. The first paragraph in the section “**General information for safe and effective use of EPZICOM** has been revised as follows:

~~**EPZICOM does not stop you from spreading HIV to other people by sex, sharing needles, or being exposed to your blood.** Talk with your healthcare provider about safe sexual practices that protect your partner. Never share needles. Do not share personal items that can have blood or body fluids on them, like toothbrushes or razor blades. 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.

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