DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20977/S-023
NDA 20978/S-027

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 Ziagen® (abacavir sulfate) Tablets (NDA 20977) and Oral Solution (NDA 20978).

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 Ziagen® (abacavir sulfate) Tablets and Oral Solution, consistent with our September 15, 2011 letter, as follows (additions are noted by underline and deletion are noted by ~~strikethrough)~~.

1. A superscript symbol, "®" has been added to the end of ZIAGEN above the Warning Box in the highlighted section of the label.

2. The phrase, "Warnings and Precautions, Immune Reconstitution Syndrome (5.3)-------(month year)" has been added under the **RECENT MAJOR CHANGES** in the Highlights section of the labeling.

3. The **DRUG INTERACTIONS** in the Highlights section of the labeling has been revised as follows:
   • Ethanol: Decreases elimination of abacavir. (7.1)
   • Methadone: An increased methadone dose may be required in a small

number of patients. (7.2)

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

WARNING: RISK OF HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS, AND SEVERE HEPATOMEGALY

Hypersensitivity Reactions: Serious and sometimes fatal hypersensitivity reactions have been associated with ZIAGEN® (abacavir sulfate).

Hypersensitivity to abacavir is a multi-organ clinical syndrome usually characterized by a sign or symptom in 2 or more of the following groups: (1) fever, (2) rash, (3) gastrointestinal (including nausea, vomiting, diarrhea, or abdominal pain), (4) constitutional (including generalized malaise, fatigue, or achiness), and (5) respiratory (including dyspnea, cough, or pharyngitis). Discontinue ZIAGEN as soon as a hypersensitivity reaction is suspected.

Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, screening for the HLA-B*5701 allele is recommended; this approach has been found to decrease the risk of hypersensitivity reaction. Screening is also recommended prior to reinitiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. HLA-B*5701-negative patients may develop a suspected hypersensitivity reaction to abacavir; however, this occurs significantly less frequently than in HLA-B*5701-positive patients.

Regardless of HLA-B*5701 status, permanently discontinue ZIAGEN if hypersensitivity cannot be ruled out, even when other diagnoses are possible.

Following a hypersensitivity reaction to abacavir, NEVER restart ZIAGEN or any other abacavir-containing product because more severe symptoms can occur within hours and may include life-threatening hypotension and death.

Reintroduction of ZIAGEN or any other abacavir-containing product, even in patients who have no identified history or unrecognized symptoms of hypersensitivity to abacavir therapy, can result in serious or fatal hypersensitivity reactions. Such reactions can occur within hours *[see Warnings and Precautions (5.1)]*.

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 ZIAGEN and other antiretrovirals *[see Warnings and Precautions (5.2)]*.

5. The phrase "*[see Warnings and Precautions (5.1), Adverse Reactions (6)]*." has been added at the end of the second paragraph in the **INDICATION AND USAGE** section of the label to be consistent with EPZICOM and TRIZIVIR as follows:

ZIAGEN is one of multiple products containing abacavir. Before starting ZIAGEN, review medical history for prior exposure to any abacavir-containing product in order to avoid reintroduction in a patient with a history of hypersensitivity to abacavir *[see Warnings and Precautions (5.1), Adverse Reactions (6)]*.

6. A bullet was added to the following sentence in the DOSAGE AND ADMINISTRATION section of the label:
    - A Medication Guide and Warning Card that provide information about recognition of hypersensitivity reactions should be dispensed with each new prescription and refill.

7. The **DOSAGE FORMS AND STRENGTH** section has been reworded to be consistent with EPZICOM and TRIZIVIR as follows:

ZIAGEN Tablets~~,~~ contain~~ing~~ 300 mg of abacavir as abacavir sulfate.~~equivalent to 300 mg abacavir,~~ The tablets are yellow, biconvex, scored, capsule-shaped, film-coated, and imprinted with "GX 623" on both sides.

ZIAGEN Oral Solution~~, each mL~~ contains~~ing~~ 20 mg/mL of abacavir as abacavir sulfate.~~equivalent to 20 mg of abacavir,~~ The solution is a clear to opalescent, yellowish, strawberry-banana-flavored liquid.

8. The **CONTRAINDICATIONS** section has been reformatted as bullets to be consistent with EPZICOM and TRIZIVIR as follows:

ZIAGEN is contraindicated in patients with:

- previously demonstrated hypersensitivity to abacavir or any other component of the products. NEVER restart ZIAGEN or any other abacavir-containing product following a hypersensitivity reaction to abacavir, regardless of HLA-B*5701 status *[see Warnings and Precautions (5.1), Adverse Reactions (6)]*.
- ~~ZIAGEN is contraindicated in patients with~~ moderate or severe hepatic impairment *[see Dosage and Administration (2.3)]*.

9. 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 ZIAGEN. 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.

10. The following texts have been added in the **ADVERSE REACTIONS** section of the label to be consistent with EPZICOM and TRIZIVIR:

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Serious and sometimes fatal hypersensitivity reaction. In one study, once-daily dosing

of abacavir was associated with more severe hypersensitivity reactions *[see Boxed Warning, Warnings and Precautions (5.1)]*.

• Lactic acidosis and severe hepatomegaly *[see Boxed Warning, Warnings and Precautions (5.2)]*.

• Immune reconstitution syndrome *[see Warnings and Precautions (5.3]*.

• Fat redistribution *[see Warnings and Precautions (5.4]*.

• Myocardial infarction *[see Warnings and Precautions (5.5)]*.

• ~~Serious and sometimes fatal hypersensitivity reactions have been associated with ZIAGEN (abacavir sulfate). In one study, once-daily dosing of ZIAGEN was associated with more severe hypersensitivity reactions *[see Warnings and Precautions (5.1)]*.~~

11. The formatting has been revised to be consistent with EPZICOM and TRIZIVIR in the **DRUG INTERACTIONS** of the label as follows:

7.1 Ethanol~~:~~

Abacavir has no effect on the pharmacokinetic properties of ethanol. Ethanol decreases the elimination of abacavir causing an increase in overall exposure *[see Clinical Pharmacology(12.3)]*.

7.2 Methadone~~:~~

The addition of methadone has no clinically significant effect on the pharmacokinetic properties of abacavir. In a study of 11 HIV-1-infected patients receiving methadone-maintenance therapy with 600 mg of ZIAGEN twice daily (twice the currently recommended dose), oral methadone clearance increased *[see Clinical Pharmacology (12.3)]*. This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients.

12. A colon (:) was added between “range” and “0.5 to 11” in the second paragraph of the **Mircobiology**/Resistance sub-section of the label and read as “range: 0.5 to 11”.

13. The formatting has been revised to be consistent with EPZICOM and TRIZIVIR in the **NONCLINICAL TOXICOLOGY/Carconogenesis, Mutagenesis, Impairment of Fertility** sub-section of the label as follows:

Carcinogenicity: Abacavir was administered orally at 3 dosage levels to separate groups of mice and rats in 2-year carcinogenicity studies. Results showed an increase in the incidence of malignant and non-malignant tumors. Malignant tumors occurred in the preputial gland of males and the clitoral gland of females of both species, and in the liver of female rats. In addition, non-malignant tumors also occurred in the liver and thyroid gland of female rats. These observations were made at systemic exposures in the range of 6 to 32 times the human exposure at the recommended dose. It is not known how predictive the results of rodent carcinogenicity studies may be for humans.

Mutagenicity: Abacavir induced chromosomal aberrations both in the presence and absence of metabolic activation in an in vitro cytogenetic study in human lymphocytes. Abacavir was mutagenic in the absence of metabolic activation, although it was not mutagenic in the presence of metabolic activation in an L5178Y mouse lymphoma assay.

Abacavir was clastogenic in males and not clastogenic in females in an in vivo mouse bone marrow micronucleus assay. Abacavir was not mutagenic in bacterial mutagenicity assays in the presence and absence of metabolic activation.

Impairment of Fertility: Abacavir had no adverse effects on the mating performance or fertility of male and female rats at a dose approximately 8 times the human exposure at the recommended dose based on body surface area comparisons.

14. In the **PATIENT COUNSELING INFORMATION/Information About Therapy With ZIAGEN** sub-section has be revised from the second paragraph as follows:

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

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 (5.4)]*.

Information About HIV-1 Infection: ZIAGEN 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 ZIAGEN. ~~Advise patients that the use of ZIAGEN 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~~ advised 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 ZIAGEN 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.

COMBIVIR, EPIVIR, EPZICOM, TRIZIVIR, and ZIAGEN are registered trademarks of ViiV Healthcare.

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.

We note that the non-safety labeling revisions in the Medication Guide will be reviewed separately because this portion have more extensive revisions than requested in our September 15, 2011 letter.

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