DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21548/S-029
NDA 22116/S-013

SUPPLEMENT APPROVAL

ViiV Healthcare Company
c/o GlaxoSmithKline, Authorized U.S. Agent
Attention: Laura C. Bacot
ID, Global Regulatory Affairs, GlaxoSmithKline
P.O. Box 13398, Five Moore Dr, Room 5.5381.5C
Research Triangle Park, NC 27709

Dear Ms. Bacot:

Please refer to your Supplemental New Drug Applications (sNDAs) dated November 11, 2011, received November 14, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lexiva® (fosamprenavir calcium) 700 mg Tablets (NDA 21548) and 50 mg/mL Oral Suspension (NDA 22116).

We acknowledge receipt of your amendments dated January 13, 2012 in response to our additional non-safety labeling change request sent on December 14, 2011 via e-mail.

We also refer to our letter dated October 19, 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 October 19, 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 Lexiva® (fosamprenavir calcium) 700 mg Tablets (NDA 21548) and 50 mg/mL Oral Suspension (NDA 22116), consistent with our October 19, 2011 letter and December 14, 2011 e-mail request, as follows (additions are noted by underline and deletions are noted by ~~strikethrough~~).

1. The phrase, “Warnings and Precautions, Immune Reconstitution (5.6) --------- (month 2012)” has been added under the **RECENT MAJOR CHANGES** in the Highlights section of the labeling.

2. The revision date has been changed from MAY 2011 to MONTH 2012 throughout the

labeling

3. The section 2.2 under the **FULL PRESCRIBING INFORMATION/CONTENTS/ DOSAGE AND ADMINISTRATION** has been revised as follows:
   2.2 Pediatric Patients (Aged 2 to 18 Years ~~years of age~~)

4. The first letter of "hypericum" in the Table 1 in the **CONTRAINDICATIONS** section of the labeling has been revised to a capital letter and it reads now as, "Hypericum".

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

   Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including LEXIVA. 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. The following portion of the Table 6 in the section 7.3 Established and Other Potentially Significant Drug Interactions has been revised as follows:

Table 6. Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration of Amprenavir or Concomitant Drug	Clinical Comment
Other Agents		
HMG-CoA reductase inhibitors: Atorvastatin[a]~~, rosuvastatin~~	↑Atorvastatin ~~↑Rosuvastatin~~	~~Use the lowest possible dose of atorvastatin or rosuvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as fluvastatin or pravastatin.~~ Titrate atorvastatin dose carefully and use the lowest necessary dose; do not exceed atorvastatin 20 mg/day.

6. The following portion of the Table 12 in the **CLINICAL PHARMACOLOGY/ Pharmacokinetics/Drug Interactions** sub-section has been revised as follows:

Table 12. Drug Interactions: Pharmacokinetic Parameters for Coadministered Drug in the Presence of Amprenavir After Administration of LEXIVA

Coadministered Drug(s) and Dose(s)	Dose of **LEXIVA**[a]	n	% Change in Pharmacokinetic Parameters of **Coadministered Drug** (90% CI)		
			C_{max}	AUC	C_{min}
Rosuvastatin 10 mg single dose	700 mg b.i.d. plus ritonavir 100 mg b.i.d. for 7 days		↑45	↑8	NA

8. The **PATIENT COUNSELING INFORMATION**/the first paragraph of **Information About Therapy With Lexiva** sub-section has been revised as follows:

~~Patients should be informed that LEXIVA is not a cure for HIV-1 infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of LEXIVA are unknown at this time. Patients should be told that there are currently no data demonstrating that therapy with LEXIVA can reduce the risk of transmitting HIV to others.~~ LEXIVA 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 LEXIVA.

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 to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** We do not know if LEXIVA 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.

9. The **PATIENT COUNSELING INFORMATION**/the second paragraph of **Information About Therapy With Lexiva** sub-section has been revised as follows:

Patients should be told that sustained decreases in plasma HIV-1 RNA have been associated with a reduced risk of progression to AIDS and death. ~~Patients should remain under the care of a physician while using LEXIVA.~~ Patients should be advised to take LEXIVA every day as prescribed. LEXIVA must always be used in combination with other antiretroviral drugs. Patients should not alter the dose or discontinue therapy without consulting their physician. If a dose is missed, patients should take the dose as

soon as possible and then return to their normal schedule. However, if a dose is skipped, the patient should not double the next dose.

10. **Patient Information**:

a. The "**LEXIVA does not**" section has been revised as follows:

- **LEXIVA does not** cure HIV-1 infection and you may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. You should remain under the care of a doctor when using LEXIVA. ~~cure HIV infection or AIDS. We do not know if LEXIVA will help you live longer or have fewer of the medical problems (opportunistic infections) that people get with HIV or AIDS. Opportunistic infections are infections that develop because the immune system is weak. Some of these conditions are pneumonia, herpes virus infections, and *Mycobacterium avium* complex (MAC) infections. It is very important that you see your healthcare provider regularly while you are taking LEXIVA. The long-term effects of LEXIVA are not known.~~
- ~~lower the risk of passing HIV to other people through sexual contact, sharing needles, or being exposed to your blood. For your health and the health of others, it is important to always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood. Never use or share dirty needles.~~

~~LEXIVA has not been fully studied in children younger than 2 years or in adults older than 65.~~

b. The second bulleted paragraph in the "**What should I tell my healthcare provider before taking LEXIVA?/**Before taking LEXIVA, tell your healthcare provider about all of your medical conditions including if you:" section has been revised as follows:

- are breastfeeding. ~~You should not breastfeed if you are HIV-positive because of the chance of passing the HIV virus to your baby through your milk. Also, it is not known if LEXIVA can pass into your breast milk and if it can harm your baby. If you are a woman who has or will have a baby, talk with your healthcare provider about the best way to feed your baby.~~ **Do not breastfeed.** We do not know if LEXIVA 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.

c. The "**What should I avoid while taking LEXIVA?**" section has been revised as follows:

- ~~Do not use certain medicines while you are taking LEXIVA. See "What is the most important information I should know about LEXIVA" and "Who should not take LEXIVA?"~~
- ~~Do not breastfeed. See "Before taking LEXIVA, tell your healthcare provider". Talk with your healthcare provider about the best way to feed your baby.~~

- ~~Avoid doing things that can spread HIV infection since LEXIVA doesn't stop you from passing the HIV 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 or razor blades.~~
- ~~Do not have any kind of sex without protection. Always practice safer sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.~~

Avoid doing things that can spread HIV-1 infection.

- **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.

LEXIVA has not been fully studied in children younger than 2 years or in adults older than 65.

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, text for the patient package insert), 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
Office of Prescription Drug Promotion (OPDP)
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 Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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
02/17/2012