DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20705/S-018

SUPPLEMENT APPROVAL

ViiV Healthcare Company
Attention: Laura Bacot, Regulatory Associate, Global Regulatory Affairs
PO Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Dear Ms. Bacot:

Please refer to your Supplemental New Drug Application (sNDA) dated July 10, 2012, received July 10, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Rescriptor® (delavirdine mesylate) Oral Tablets, 100 mg and 200 mg.

We acknowledge receipt of your amendments dated July 20 and August 6, 2012.

We also refer to our letter dated June 14, 2012, 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 revised drug-drug interaction information based on additional review of drug-drug interaction data and 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 requested in our June 14, 2012 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 provides for revisions to the labeling for Rescriptor® (delavirdine mesylate) Oral Tablets, 100 mg and 200 mg, consistent with our June 14, 2012 letter as follows (additions are noted by underline and deletions are noted by ~~strikethrough~~).

1. The **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 RESCRIPTOR. 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.

2. The third, fourth, and fifth sentences in the **PRECAUTIONS/Information for Patients** sub-section has been revised as follows:

Patients should be informed that RESCRIPTOR is not a cure for HIV-1 infection and ~~that they~~ patients may continue to ~~acquire~~ experience illnesses associated with HIV-1 infection, including opportunistic infections. ~~Treatment with RESCRIPTOR has not been shown to reduce the incidence or frequency of such illnesses, and p~~Patients should be advised to remain under the care of a physician ~~when using~~ while taking RESCRIPTOR. ~~Patients should be advised that the use of RESCRIPTOR has not been shown to reduce the risk of transmission of HIV-1.~~

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 RESCRIPTOR 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.

3. The Table 7, in the **PRECAUTIONS/Drug Interactions** sub-section, has been revised as follows:

Table 7. Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration of Delavirdine or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents: Nucleoside Reverse Transcriptase Inhibitor		

~~Amprenavir~~	~~↑Amprenavir~~	~~Appropriate doses of this combination with respect to safety, efficacy, and pharmacokinetics have not been established.~~
Didanosine[a]	↓Delavirdine ↓Didanosine	Administration of didanosine (buffered tablets) and RESCRIPTOR should be separated by at least 1 hour.
HIV-Antiviral Agents: Non-nucleoside Reverse Transcriptase Inhibitors		
NNRTI	↔Delavirdine ↑NNRTI	Combining ~~two~~NNRTIs has not been shown to be beneficial. RESCRIPTOR should not be coadministered with another NNRTI.
HIV-Antiviral Agents: Protease Inhibitors		
Indinavir[a]	↑Indinavir	A dose reduction of indinavir to 600 mg 3 times daily should be considered when RESCRIPTOR and indinavir are coadministered.
Lopinavir/Ritonavir	↑Lopinavir ↑Ritonavir	Appropriate doses of this combination with respect to safety, efficacy, and pharmacokinetics have not been established.
Nelfinavir[a]	↑Nelfinavir ↓Delavirdine	Appropriate doses of this combination with respect to safety, efficacy, and pharmacokinetics have not been established (see CLINICAL PHARMACOLOGY: Tables 1 and 2).
Ritonavir	↑Ritonavir	Appropriate doses of this combination with respect to safety, efficacy, and pharmacokinetics have not been established.
Saquinavir[a]	↑Saquinavir	A dose reduction of saquinavir (soft gelatin capsules) may be considered when RESCRIPTOR and saquinavir are coadministered (see CLINICAL PHARMACOLOGY: Table 1). Appropriate doses with respect to safety, efficacy, and pharmacokinetics have not been established.
HIV-Antiviral Agents: CCR5 Inhibitor		
Maraviroc	↑Maraviroc	Concomitant use of RESCRIPTOR and maraviroc has not been studied. However, RESCRIPTOR is a potent CYP3A4 inhibitor and the maraviroc dose ~~of SELZENTRY dose~~ should be reduced during coadministration. Refer to the full prescribing information for maraviroc (SELZENTRY) ~~label~~ for dosing recommendations.

↑ Indicates increase.
↓ Indicates decrease.

[a]The interaction between RESCRIPTOR and the drug was evaluated in a clinical study. All other drug interactions shown are predicted. ~~See CLINICAL PHARMACOLOGY for magnitude of interaction, Tables 1 and 2.~~

4. The end section of package insert and the **Patient Information** have been revised as follows:

~~April 2012~~Month Year
RES: ~~2~~PI

5. **Patient Information**:

a. The word, HIV, has been revised as HIV-1 for consistency with FDA requested new text throughout the **Patient Information** section of the label.

b. The "**Does RESCRIPTOR cure HIV or AIDS?**" and "**Does RESCRIPTOR reduce the risk of passing HIV to others?**" sections have been deleted and replaced with a "**General information about RESCRIPTOR**" section, as follows:

~~**Does RESCRIPTOR cure HIV or AIDS?**~~

~~**RESCRIPTOR is not a cure for HIV infection or AIDS. People taking RESCRIPTOR may still develop opportunistic infections or other conditions associated with HIV infection. Opportunistic infections are infections that develop because the immune system is weak. Some of these conditions are pneumonia, herpes virus infections, *Mycobacterium avium* complex (MAC) infections, and Kaposi's sarcoma.**~~

General information about RESCRIPTOR

RESCRIPTOR does not cure HIV-1 or AIDS 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 RESCRIPTOR.

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 to lower the chance of sexual contact with semen, vaginal secretions, or blood.

~~**Does RESCRIPTOR reduce the risk of passing HIV to others?**~~
~~**RESCRIPTOR does not reduce the risk of transmitting HIV to others through sexual contact or blood contamination. Continue to practice safe sex and do not use or share dirty needles.**~~

c. The fourth bulleted paragraph in the "**Who should not take RESCRIPTOR?**" section has been revised as follows:

> If you are breastfeeding, ~~it is very important that you speak with your healthcare provider about the best way to feed your baby. If your baby does not already have HIV, there is a chance that it can be transmitted through breast-feeding.~~ **~~The Centers for Disease Control and Prevention recommends that women with HIV do not breast-feed.~~ do not breastfeed.** We do not know if RESCRIPTOR 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. Talk with your ~~doctor~~ healthcare provider about the best way to feed your baby.

We have completed our review of this supplemental application. 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, text for the Patient Information), 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
08/10/2012