DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20564/S-033
NDA 20596/S-032

SUPPLEMENT APPROVAL

ViiV Healthcare Company
Attention: Vicki Horton, DVM, Ph.D., DABT
Director, Global Regulatory Affairs
Five Moore Drive, PO Box 13398
Research Triangle Park, NC 27709

Dear Dr. Horton:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received May 23, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for EPIVIR (lamivudine) 150 mg scored tablets, 300 mg tablets and 10 mg per mL oral solution.

We acknowledge receipt of your amendments dated June 20, 2014, July 29, 2014, November 19, 2014, December 10, 2014, February 26, 2015, March 4, 2015, March 13, 2015, March 20, 2015, and March 23, 2015.

These "Prior Approval" supplemental new drug applications provide for once-daily dosing in pediatric patients 3 months of age and older in combination with other antiretroviral agents for the treatment of HIV-1 infection.

APPROVAL & LABELING

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.

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 and 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 that include labeling changes 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).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

This product is appropriately labeled for use in ages 3 months to 17 years for this indication. Therefore, no additional studies are needed in this pediatric group.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since EPIVIR (lamivudine) was approved on November 17, 1995, we have become aware of lower lamivudine exposures in pediatric subjects receiving the oral solution compared to the tablet formulation across trials. The review of data from the ARROW trial also documents lower treatment response rates in younger subjects receiving the oral solution. These results suggest that in pediatric patients lower lamivudine exposures produced by the oral solution may contribute to the potential for a significant safety risk of viral resistance caused by suboptimal drug concentrations. Viral resistance generally leads to treatment failure and decreased therapeutic options in the future. The reasons for the lower exposure following administration of EPIVIR (lamivudine) oral solution are not known but the current review suggests a possible interaction with other solution/suspension medications.

In addition, we have become aware of substitutions in reverse transcriptase, K65R, L74V, M184V/I and Y115F, that confer reduced susceptibility to abacavir and of substitution M184V/I that confers high level reduced susceptibility to lamivudine.

We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the unexpected serious risk of the development of resistance in pediatric patients who received EPIVIR (lamivudine) oral solution, and the emergence of resistance-associated substitutions in HIV-1 isolates from subjects who fail to respond to the treatment regimen.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

2889-1 Analyze the emergence of resistance-associated substitutions in HIV-1 isolates from subjects who fail to respond to the treatment regimen in the ARROW trial. Conduct genotypic analyses of the isolates to identify and characterize HIV-1 mutants with, but not limited to, the substitutions K65R, L74V, M184V/I, and Y115F in reverse transcriptase. In addition, submit the ARROW trial resistance data and plots of viral load data from virologic failure subjects.

The timetable you submitted on March 4, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: 05/31/2015

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify the potential mechanism(s) associated with the observation of suboptimal drug concentrations which may lead to an unexpected serious risk for the development of resistance in subjects who receive EPIVIR (lamivudine) oral solution concomitantly with other oral medications containing sorbitol.

Therefore, based on the available scientific data, FDA has determined that you are required to conduct the following:

2889-2 A drug interaction trial to determine the effects of sorbitol-containing solutions on lamivudine exposure following administration of lamivudine oral solution. Evaluate bioavailability differences between lamivudine solution administered alone and in combination with other oral solutions containing sorbitol. If an interaction is found, provide an assessment of the potential clinical impact of the interaction and if warranted, provide a revised dosing recommendation for pediatric patients taking lamivudine oral solution.

The timetable you submitted on March 20, 2015 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/30/2015
Trial Completion:	04/30/2016
Final Report Submission	11/30/2016

Submit the protocol to your IND 63468, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii), requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

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/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at

http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. 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 Victoria Tyson, Regulatory Project Manager, at (301) 796-0827.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
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/

DEBRA B BIRNKRANT
03/23/2015