DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021356/S-034 **SUPPLEMENT APPROVAL**

GILEAD SCIENCES, INC.
Attention: Nikki McMillan
Senior Manager, Regulatory Affairs
4 University Place
4611 University Drive, Building 4
Durham, NC 27707

Dear Ms. McMillan:

Please refer to your Supplemental New Drug Application (sNDA) dated September 30, 2009, received October 1, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VIREAD® (tenofovir disoproxil fumarate), 300 mg Tablets.

We acknowledge receipt of your submissions dated October 15, 2009, November 12, 2009, December 23, 2009, February 5, 2010, April 8, 2010, May 12, 2010, June 17, 2010, July 22, 2010, July 30, 2010, August 30, 2010, September 10, 2010 and September 27, 2010.

This Prior Approval supplemental new drug application was submitted to include information in the label regarding VIREAD® (tenofovir disoproxil fumarate) treatment of chronic hepatitis B (CHB) in adult patients with decompensated liver disease based on data from clinical trial GS-US-174-0108.

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, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (package insert, patient package insert) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. 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 pending "Changes Being Effected" (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.

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable because there are too few children with decompensated liver disease to study and they are geographically dispersed.

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 VIREAD® (tenofovir disoproxil fumarate) was approved on October 26, 2001, we have become aware of a potential renal safety signal with VIREAD® (tenofovir disoproxil fumarate) in our review of the safety data from clinical trial GS-US-174-0108. A higher proportion of VIREAD® (tenofovir disoproxil fumarate) exposed subjects experienced an increase in serum creatinine $\geq$ 0.5 mg/dL over baseline, and a creatinine clearance < 50 mL/min in this small trial than in the larger trials GS-US-0102 and 0103 in subjects with compensated liver disease. However, trial GS-US-174-0108 was too small to allow adequate evaluation of these events. In addition, we recognize both VIREAD® (tenofovir disoproxil fumarate) and decompensated liver disease may result in renal impairment and distinguishing the relative contributions of each in the development of hepatorenal syndrome may be difficult. We consider this information to be "new safety information" as 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 assess a signal of a serious risk of increased risk for tenofovir-associated renal toxicity in patients with decompensated liver disease.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

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

1687-1 Conduct a prospective 5-year pre-OLT (orthotopic liver transplant) registry study to collect and analyze data regarding renal function in patients with chronic hepatitis B and decompensated liver disease treated with VIREAD® (tenofovir disoproxil fumarate) and a comparator group taking another nucleoside analogue, such as entecavir.

The timetable you submitted on September 10, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission: April 2011
Study Completion: December 2016
Interim reports: December 2012
December 2013
December 2014
December 2015
Final Report Submission: June 2017

Submit the protocol to your IND 52,849, 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, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and 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.(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

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

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 Carrie Ceresa, Pharm D., MPH, Regulatory Project Manager, at (301) 796-4108.

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/

JEFFREY S MURRAY
10/01/2010