DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-356/S-033 **SUPPLEMENT APPROVAL**

Gilead Sciences, Inc.
Attention: Dara Wambach, MA
Senior Manager, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Wambach:

Please refer to your supplemental new drug application dated and received on September 25, 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 27, 2009, November 24, 2009, December 3, 2009, December 11, 2009, January 8, 2010, January 27, 2010, February 2, 2010, March 19, 2010 and March 22, 2010.

This Prior Approval supplemental new drug application was submitted to expand the indication to include the treatment of HIV infection in combination with other antiretroviral agents in patients 12 to less than 18 years of age based on 48-week clinical data from Study GS-US-104-0321.

We have completed our review of this 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

Within 14 days from the date of this letter, please 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 structured product labeling (SPL) format that includes the changes approved in this supplemental application.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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 note that you have fulfilled the pediatric study requirement for evaluating treatment of HIV infection in pediatric patients 12 to < 18 years of age for this application.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (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 (section 505(o)(3)(A)).

Since VIREAD® (tenofovir disoproxil fumarate) was approved on October 26, 2001, we have become aware of new safety information related to the treatment of HIV-1 with VIREAD in adolescents. In study GS-US-104-0321, evidence of impaired bone mineral density (BMD) gains and perturbations of bone deposition and resorption, similar to those identified in the adult HIV-1 treatment trials with VIREAD (tenofovir disoproxil fumarate), was observed. We consider this information to be "new safety information" as defined in FDAAA.

Adolescence is a period of rapid bone growth important to adult bone health and the impact of these changes in growing adolescents and younger pediatric patients on future fracture risk is not known. The etiology of VIREAD's (tenofovir disoproxil fumarate) bone effects (whether direct or secondary) remains unclear. Based on the clinical trials data and postmarketing reports, the bone effects may be related to proximal renal tubule dysfunction and/or may be due to direct effects on osteoblast and osteoclast function.

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 elucidate the relationship between BMD changes and proximal renal tubulopathy.

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 this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to gain understanding of the mechanism(s) leading to decreases in BMD so that monitoring for detection of BMD abnormalities and appropriate management recommendations can be developed.

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

1618-1 Conduct a controlled trial (trial of pediatric HBV-infected subjects required under PREA) that elucidates the mechanism of tenofovir's effects on bone. Evaluations of adequate numbers of pediatric subjects must include the following:

a. Measurement of renal excretion of calcium, phosphorous, and magnesium through calculation of the renal phosphate threshold (TmP/GFR).

b. Measurement of urine bicarbonate, urine n-telopeptide, serum bone-specific alkaline phosphatase, parathyroid hormone, osteocalcin, c-telopeptide, 25 hydroxyvitamin D, 1,25 (dihydroxyvitamin) D levels, albumin, calcium, phosphate, magnesium, and bicarbonate.

c. Correlation of renal parameters with measurements of bone mineral density (DEXA).

The timetable you submitted on March 24, 2010, states that you will conduct this study according to the following schedule:

Protocol Submission:	July, 2011
Trial Completion:	June, 2015
Final Report Submission:	December, 2015

Submit the protocol to your IND, with a cross-reference letter to this NDA. Submit all final report(s) 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)**

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of the postmarketing commitment in your submission dated March 22, 2010. This commitment is listed below.

1618-2 Conduct *in vitro* studies in caco-2 cells to evaluate a potential inhibitory effect of tenofovir DF on absorption of phosphate in the GI tract, and assess the applicability of the study findings on the observed nonclinical and clinical effects of tenofovir DF on BMD.

Protocol Submission:	July, 2010
Study Completion:	December, 2010

Final Report Submission: February, 2011

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 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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see 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 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 an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
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

Enclosures: Content of Labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21356	SUPPL-33	GILEAD SCIENCES INC	VIREAD(TENOFOVIR DISOPROXIL FUMARATE)300

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
03/24/2010