CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-356

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-356

Gilead Sciences, Inc
Attention: Rebecca Coleman, Pharm D
333 Lakeside Drive
Foster City, California 94404

Dear Dr. Coleman:

Please refer to your new drug application (NDA) dated April 30, 2001, received May 1, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VIREAD™ (tenofovir disoproxil fumarate) 300 mg Tablets.

We acknowledge receipt of your submissions dated:

March 21, 2001	June 22, 2001	August 13, 2001	October 2, 2001
April 12, 2001	July 5, 2001	August 14, 2001	October 16, 2001
April 30, 2001	July 13, 2001	August 16, 2001	October 17, 2001
May 7, 2001	July 16, 2001	August 21, 2001	October 18, 2001
May 11, 2001	July 17, 2001	August 22, 2001	October 19, 2001
May 15, 2001	July 18, 2001	August 23, 2001	October 22, 2001
May 24, 2001	July 30, 2001	August 29, 2001	October 23, 2001
June 6, 2001	August 1, 2001	August 30, 2001	October 24, 2001
June 8, 2001	August 2, 2001	September 5, 2001	October 25, 2001
June 12, 2001	August 3, 2001	September 6, 2001	October 26, 2001
June 19, 2001	August 7, 2001	September 20, 2001	

This new drug application provides for the use of VIREAD™ (tenofovir disoproxil fumarate) 300 mg Tablets in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults.

We have completed the review of this application, as amended, according to the regulations for accelerated approval (21 CFR 314.510), and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed-upon labeling text. Accordingly, the application is approved effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced accelerated approval regulations.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, immediate container and carton labels.) Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of FPL electronically according to the guidance for industry entitled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999.) Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavyweight paper or similar material. For administrative purposes, this submission should be designated **"FPL for Approved NDA 21-356."** Approval of this submission by FDA is not required before the labeling is used.

Products approved under the accelerated approval regulations require further adequate and well-controlled studies to verify and describe clinical benefit. We remind you of your postmarketing studies (Subpart H) as specified in your submission dated October 26, 2001 in which you agreed to submit the results from the final study analyses of the following two phase-3 studies of the safety and efficacy of VIREAD™ to support traditional approval:

- Study GS-00-903, *"A Phase III, Double-Blind, Randomized, Active-Controlled, Multicenter Study of the Treatment of Antiretroviral-Naïve HIV-1 Infected Patients Comparing Tenofovir Disoproxil Fumarate Administered in Combination with Lamivudine and Efavirenz Versus Stavudine, Lamivudine, and Efavirenz,"* is currently underway.

- Study GS-01-928, *"A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Tenofovir Disoproxil Fumarate Plus an Optimized Background Regimen (OBR) Versus OBR Alone in HIV-1 infected, Antiretroviral Treatment-Experienced Children,"* is expected to begin enrollment in March 2002.

In addition, you are required to submit complete analyses of the safety data with respect to bone effects from studies 903 and 928. For study 928, it is excepted that you will collect data on bone mineral density (BMD) and laboratory parameters specific to bone metabolism, including, but not limited to, osteocalcin, bALP, N and C-teleopeptide, vitamin D and PTH. The final study reports for both studies should include detailed analyses of the BMD results and the laboratory parameters specific to bone metabolism, including but not limited to osteocalcin, bALP, N and C- teleopeptide, vitamin D and PTH. The final study reports for GS-00-903 and GS-01-928 should include analyses for these parameters through week 96 and 48, respectively. In addition, the final study report for study 903 should include analyses to address the potential for long term renal toxicities (through week 96).

Projected Submission Date: Two reports are planned for Study 903, one following completion of the first 48 weeks and a second following completion of 96 weeks. The 48-week report will be submitted in 2Q 2002; the final (96-week) report will be submitted in 2Q 2003. The final study report for Study 928 will be submitted in 2Q 2004.

In addition, please note the following postmarketing commitments as specified in your submission dated October 26, 2001. These commitments, along with any completion dates agreed upon, are listed below.

Microbiology:

1. Conduct genotypic and phenotypic analyses of clinical isolates from all adult and pediatric patients in Studies 903 and 928 who experience loss of virologic response.

Projected Submission Date: Analysis of the virologic data in Studies 903 and 928 will be completed at the same time as the Clinical Study Reports. Two virology reports are planned for Study 903, one following completion of the first 48 weeks and a second following completion of 96 weeks. The 48-week report will be submitted in 2Q 2002; the final (96-week) report will be submitted in 2Q 2003. The final study report for Study 928 will be submitted in 2Q 2004.

2. Evaluate the virologic response of VIREAD in patients with baseline reduced susceptibility to didanosine and abacavir. Isolates with mutations conferring resistance to didanosine or abacavir should be evaluated in order to discern meaningful differences in virologic response.

3. Characterize the role of the K65R mutation in conferring resistance to VIREAD and cross resistance between VIREAD and other nucleoside reverse transcriptase inhibitors, specifically didanosine, abacavir and zalcitabine.

4. Investigate whether the M184V increases virologic response, if present alone or in combination with other NRTI mutations. Isolates should be evaluated in order to discern meaningful differences in virologic response.

   Projected Submission Date: The post-approval commitments 2-4 will be included in the virology analyses for Studies 903 and 928 (as appropriate). Results of the analyses will be included in the virology study reports. Analysis of the virologic data in Studies 903 and 928 will be completed at the same time as the Clinical Study Reports. Two virology reports are planned for Study 903, one following completion of the first 48-weeks and a second following completion of 96 weeks. The 48-week report will be submitted in 2Q 2002; the final (96 week) report will be submitted in 2Q 2003. The final study report for Study 928 will be submitted in 2Q 2004.

Pharmacology/toxicology

5. Carcinogenicity studies in rats and mice.

   Projected Submission Date: Final reports will be submitted by 4Q 2002 (rat) and 3Q 2003 (mouse).

Clinical Pharmacology:

6. Evaluation of VIREAD pharmacokinetics in subjects with renal insufficiency, to allow the determination of dosing recommendations.

   Projected Submission Date: A protocol for Study 919 has been submitted to the Agency; a final study report will be submitted 4Q 2002.

7. Measurement of concentrations of tenofovir disoproxil and mono-POC PMPA relative to tenofovir in vivo.

   Projected Submission Date: Gilead is currently developing the assays required to evaluate the prodrug and mono-POC species. Upon completion of the validation, Gilead intends to conduct this testing using samples from either an ongoing or planned study, in consultation with the reviewing Division. Final results will be submitted 2Q 2003.

8. Characterization of the specific renal transport pathways of tenofovir *in-vivo* (anionic vs. cationic transport). Once determined, evaluate the potential for drug interactions between VIREAD and drugs that are renally eliminated and frequently used by the HIV population. Specific examples may include acyclovir, valacyclovir, ganciclovir, valganciclovir and

cidofovir. The study design should mimic clinical conditions with regard to dosing with/without food.

Projected Submission Date: Gilead will provide the reviewing Division with a summary review of the renal transport mechanism along with a plan for further studies in 1Q 2002. Final study reports from any clinical studies conducted to answer the question of an interaction will be submitted 6 months following completion of the *in-vivo* (human) sampling.

9. Conduct drug interaction studies between VIREAD and enteric-coated didanosine, methadone, oral contraceptives and adefovir dipivoxil. The study design should mimic clinical conditions with regard to dosing with/without food.

   Projected Submission Date: Results from these drug interaction studies will be submitted in 3Q 2002.

10. Conduct a drug interaction study including VIREAD™ and lopinavir/ritonavir to confirm lopinavir/ritonavir PK changes observed in Study 909. The study design should mimic clinical conditions with regard to dosing with/without food. If these pharmacokinetic changes are confirmed, conduct a drug interaction study between VIREAD™ and ritonavir 400 mg to better characterize the drug interaction observed between VIREAD™ and higher doses of ritonavir.

    Projected Submission Date: In 4Q 2001, Gilead will propose a study to the reviewing Division that re-examines the potential for interaction between VIREAD™ and Kaletra. A study report will be submitted in 1Q 2003. If indicated, a proposal for further study of a potential interaction between ritonavir and VIREAD™ will be outlined.

Clinical

11. Evaluation of the activity (hepatitis B DNA, hepatitis e antigen seroconversion and effect on transaminases) and safety of VIREAD™ for the treatment of hepatitis B infection in patients who are coinfected with HIV and hepatitis B. Specifically, the occurrence of hepatitis flares in patients who discontinue VIREAD™ treatment will be monitored. The occurrence of tenofovir associated hepatitis B resistance should also be evaluated. The above parameters should be evaluated in patients receiving the combination of lamivudine and VIREAD™ for the treatment of hepatitis B. Approximately 100 patients receiving VIREAD™-containing regimens should be evaluated from planned and ongoing studies. Data from comparator arms should also be submitted for review.

    Projected Submission Date: A summary of the hepatitis B experience from Studies 902, 907, and 903 (48 week) will be submitted 4Q 2002. Data from the planned ACTG 5127 study will be submitted in 4Q 2004.

12. Long-term safety monitoring for serious adverse events and fractures in study 910, including BMD changes in patients participating in the BMD substudy. This study will follow approximately 575 patients for up to four years.

    Projected Submission Date: A final report for Study 910 will be submitted 3Q 2003.

Please submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected

summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, the number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."** Also, please designate these submissions as **"Subpart H."**

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

As of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens must contain an assessment of the safety and effectiveness of the product in pediatric patients unless FDA waives or defers the requirement (63 *FR* 66632) (21 CFR 314.55.) We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 21 CFR 601.27) for pediatric patients under the age of 18 years. Accordingly, we are deferring submission of your studies in pediatric patients under the age of 18 years until November 1, 2004.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Also, please submit one market package of the drug product when it is available.

If you have any questions, call Marsha Holloman, Regulatory Health Project Manager, at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

Mark Goldberger, MD, MPH
Acting Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Attachments: Final Labeling