DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 52,849
NDA 21-356

Gilead Sciences, Inc
Attention: Rebecca Coleman, Pharm D
Director, Regulatory Affairs
333 Lakeside Drive
Foster City, CA 94404

Dear Dr. Coleman:

Please refer to your investigational new drug (IND) 52,849 for tenofovir DF (PMPA ProDrug) for the treatment of HIV infection dated March 18, 1997. Also, 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. Finally, reference is made to your Proposed Pediatric Study Request (PPSR) submitted on September 6, 2001 to NDA 21-356, Serial No. 066.

To obtain needed pediatric information on tenofovir disoproxil fumarate, the Food and Drug Administration (the Agency) is hereby making a formal Written Request (WR), pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies:

- ***Type of study(ies):***
  1. Multiple-dose pharmacokinetic, safety and activity study (ies) of tenofovir disoproxil fumarate in combination with other antiretroviral agents in HIV-infected, antiretroviral therapy-experienced, pediatric patients.

     The objective of these studies will be to determine the pharmacokinetic and safety profile of tenofovir across the age range studied and identify the appropriate dose for use in HIV-infected children.
  2. Randomized controlled safety and efficacy study (ies) of tenofovir in combination with other antiretroviral agents in HIV-infected, antiretroviral therapy-experienced, pediatric patients.
- ***Indication to be studied****:*

  Treatment of HIV infection in children
- ***Age group in which study(ies) will be performed:***

  HIV-infected pediatric patients from 2 to 18 years
- ***Drug Information***

  Dosage form: 75, 150, and 300 mg tablets and an age appropriate-formulation. The studies described above should use an age-appropriate formulation of tenofovir disoproxil fumarate. The relative bioavailability of this formulation should be determined and compared with the marketed

formulation of VIREAD™ (tenofovir disoproxil fumarate) 300 mg Tablets. Full study reports of any relative bioavailability studies should be submitted to the Agency. If an age-appropriate formulation cannot be developed, complete documentation of your attempts and a detailed explanation of why the attempts were unsuccessful should be submitted. Under these circumstances other formulations can be used, if they are standardized, palatable, and shown in adults to be of acceptable relative bioavailability (compared with the marketed product.)

Route of administration: oral

Regimen: to be determined by development program

- ***Drug specific safety concerns:***

  Drug specific safety issues arising from preclinical testing and clinical trials performed in HIV-infected adults must be addressed in an adequate number of pediatric patients. Please collect and submit data reviewing the following in children:

  1. Gastrointestinal symptoms
  2. Potential for long term renal toxicity, including increases in serum creatinine and decreases in serum phosphorus over 48 weeks of dosing
  3. Potential for bone effects, including but not limited to the following parameters, bone mineral density, osteocalcin, bone-specific alkaline phosphatase, N and C- teleopeptide, Vitamin D levels and parathyroid hormone levels over 48 weeks of dosing
  4. Potential for growth abnormalities
  5. Bone fractures and healing

- ***Statistical information, including power of study and statistical assessments:***

  1. Descriptive analyses of multiple-dose pharmacokinetic, safety and activity data in HIV-infected pediatric patients. A minimum number of pediatric patients (as stated below) should complete the pharmacokinetic study (ies) conducted to characterize pharmacokinetics for dose selection. Final selection of sample size for each age group should take into account all potential sources of variability. As study data are evaluated, the sample size should be increased as necessary for characterization of pharmacokinetics across the intended age range.

     2 years to < 6 years: 12

     6 years to < 12 years: 8

     12 years to 18 years: 6

  2. Efficacy trial(s) should be of sufficient size to detect clinically meaningful differences in efficacy and toxicity between the treatment arms.
  3. Safety of tenofovir should be evaluated in an adequate number of children to characterize adverse events across the age range studied (approximately 100 children).

- ***Study Endpoints:***

  1. Pharmacokinetic parameters such as C_{max}, C_{min}, $T_{max,}$ $T_{1/2}$, AUC.
  2. Safety and tolerability: HIV-infected pediatric patients should be followed for safety for a minimum of 48 weeks at the recommended dose. In addition, please also submit plans for long-term safety monitoring in HIV-infected pediatric patients who have received tenofovir

disoproxil fumarate, particularly with regard to bone growth, incidence of fractures and renal toxicity.

3. Activity: Assessment of changes in plasma HIV-RNA levels and in CD4 cell counts.
4. Resistance: Collect and submit information regarding the resistance profile (genotypic and phenotypic) of clinical isolates from pediatric patients receiving tenofovir at baseline and from pediatric patients who experience a loss of virologic response during treatment.

- ***Labeling that may result from the study(ies):***

  Information regarding dosing, safety, and activity in HIV-infected pediatric population.

- ***Format of reports to be submitted:***

  Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. Please include other information as appropriate.

- ***Timeframe for submitting reports of the study(ies):***

  Reports of the above studies must be submitted to the Agency on or before November 1, 2004. Please keep in mind that pediatric exclusivity only extends existing patent protection or exclusivity that has not expired or been previously extended at the time you submit your reports of the studies in response to this Written Request.

Please submit protocols for the above studies to the IND and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a supplement to your approved NDA or as a new drug application, as appropriate, with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773
.
If you wish to discuss any amendments to this WR, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, contact 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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mark Goldberger

12/21/01 09:34:56 AM