



NDA 21-356
IND 52,849

AMENDED WRITTEN REQUEST LETTER

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

Dear Ms. Wambach,

Please refer to your correspondence dated November 20, 2007, requesting changes to FDA's December 21, 2001 Written Request, as amended October 29, 2004, for pediatric studies for VIREAD (tenofovir disoproxil fumarate, TDF).

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on December 21, 2001, as amended on October 29, 2004, remain the same.

Types of Studies:

2. Randomized, ~~open-label~~ **safety**, and activity study(ies) of VIREAD™ (tenofovir disoproxil fumarate) in combination with other antiretroviral agents in HIV-infected, antiretroviral therapy-experienced, pediatric patients through at least 48 weeks of dosing.

Drug Information:

*Dosage forms: 75, 150, ~~and~~ **or** 300 mg tablets and age appropriate-formulation*

Study Endpoints:

Resistance

Collect and submit information regarding the resistance profile (~~genotypic and phenotypic~~) of clinical isolates at baseline, **as appropriate**, and during treatment from pediatric patients receiving VIREAD™ (tenofovir disoproxil fumarate), particularly from those who experience loss of virologic response.

Timeframe for submitting reports of the studies:

Collect and submit information regarding the resistance profile Reports of the studies that meet the terms of the Written Request Letter dated December 21, 2001, as amended by letter October 29, 2004 and as amended by this letter, must be submitted to the agency on or before ~~January 31, 2008~~ **September 30, 2009** in order to possibly qualify for pediatric exclusivity under Section 505A of the Act. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or

exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, 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. In addition, send a copy of the cover letter of your submission, via fax (301-827-5911) 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 Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **“PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES”** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

If (1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval), (2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act, and (3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice in accordance with section 505A(e)(2).

Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that tenofovir disoproxil fumarate is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies).

In accordance with section 505A(k)(1) of the Act, the Agency must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. The type of response to the Written Request (i.e., complete or partial response);
2. The status of the application (i.e., withdrawn after the supplement has been filed or pending);
3. The action taken (i.e. approval, approvable, not approvable); or
4. The exclusivity determination (i.e., granted or denied).

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Finally, please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on these requirements and the submission of this information can be found at www.ClinicalTrials.gov.

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, call Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, at 301-796-0731.

Sincerely,

{See appended electronic signature page}

Edward M. Cox, MD, MPH
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Attachment (Complete Copy of Written Request as Amended)



AMENDED WRITTEN REQUEST

NDA 21-356

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

Dear Ms. Wambach:

Please refer to your correspondence dated November 20, 2007, requesting changes to FDA's December 21, 2001 Written Request, as amended October 29, 2004, for pediatric studies for VIREAD (tenofovir disoproxil fumarate, TDF).

To obtain needed pediatric information on VIREAD (tenofovir disoproxil fumarate), the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the following studies. This revised Written Request supersedes any and all earlier versions.

Type of studies:

1. Multiple-dose pharmacokinetic, safety, and activity study(ies) of VIREAD (tenofovir disoproxil fumarate) in combination with other antiretroviral agents in HIV-infected, antiretroviral therapy-experienced, pediatric patients.
2. Randomized safety and activity study(ies) of VIREAD (tenofovir disoproxil fumarate) in combination with other antiretroviral agents in HIV-infected, antiretroviral therapy-experienced, pediatric patients through at least 48 weeks of dosing.

The objective of these studies will be to determine the pharmacokinetic and safety profile of VIREAD (tenofovir disoproxil fumarate) across the age range studied, identify an appropriate dose (or doses) for use in HIV-infected pediatric patients, and evaluate the activity of this dose (or doses) in treatment regimens.

Indication to be studied:

Treatment of HIV infection in pediatric patients

Age group in which studies will be performed:

HIV-infected pediatric patients from 2 to 18 years

Drug Information:

Dosage forms: 75, 150, or 300 mg tablets and age appropriate-formulation.

Route of administration: oral

Regimen: to be determined by development program

Use an age-appropriate formulation in the study(ies) described above. If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients.

Development of a commercially-marketable formulation is preferable. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.

If you cannot develop a commercially marketable age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies should be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

Drug specific safety concerns:

Based on available toxicity information with your product, please provide specific safety parameters that your pediatric program will address including:

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-telopeptide, Vitamin D levels, and parathyroid hormone levels over 48 weeks of dosing;
4. Potential for growth abnormalities; and

5. Bone fractures and healing.

Safety of VIREAD™ (tenofovir disoproxil fumarate) must be studied in an adequate number of pediatric patients to characterize adverse events across the age range, approximately 100 pediatric patients.

Statistical information, including power of study and statistical assessments:

Descriptive analyses of multiple-dose pharmacokinetic, safety and activity data in HIV-infected pediatric patients. A minimum number of pediatric patients (as stated below) will 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

Studies must include an adequate number of patients to characterize pharmacokinetics and select a therapeutic dose for the age ranges studied, taking into account inter-subject and intra-subject variability. The number of patients should be generally well distributed across the age range studied.

Study Endpoints:

Pharmacokinetics

Parameters such as C_{max}, C_{min}, T_{max}, t_{1/2}, AUC, and apparent oral clearance.

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 VIREAD™ (tenofovir disoproxil fumarate) particularly with regard to bone growth, incidence of fractures, and renal toxicity.

Activity

Assessment of changes in plasma HIV RNA levels and in CD4 cell counts.

Resistance

Collect and submit information regarding the resistance profile of clinical isolates at baseline, as appropriate, and during treatment from pediatric patients receiving VIREAD™ (tenofovir disoproxil fumarate), particularly from those who experience loss of virologic response.

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. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian, or other Pacific Islander, or White. For ethnicity one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino. 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 September 30, 2009. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Response to Written Request:

As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (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 new drug application or as a supplement to your approved NDA 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.

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If you have any questions, contact Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager, at 301-796-0731.

Sincerely yours,

{See appended electronic signature page}

Edward M. Cox, MD, MPH
Director
Office of Antimicrobial Products
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/

Edward Cox
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