DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST – AMENDMENT #5

IND 58,627
NDA 21-548
NDA 22-116

ViiV Healthcare Company
Attention: Susan L. Watts, Ph.D.
Director, Global Regulatory Affairs
Five Moore Drive, P.O. Box 13398, Room 5.5381.5C
Research Triangle Park, NC 27709

Dear Dr. Watts:

Please refer to your correspondence dated November 22, 2010, requesting changes to FDA's December 26, 2001 Written Request for pediatric studies for LEXIVA® (fosamprenavir calcium).

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 26, 2001, and as amended on January 10, 2003, June 19, 2003, August 14, 2006 and December 23, 2009, remain the same.

Type of studies:

Multiple-dose pharmacokinetic and safety study of GW433908 in combination with low-dose ritonavir (RTV) in HIV-infected pediatric patients 4 weeks to 17 years old. Multiple-dose pharmacokinetic assessment of GW433908 (without RTV) to determine a recommended dose in HIV-infected pediatric patients ~~4 weeks~~ 2 to 5 years old.

The objective of these studies will be to determine the pharmacokinetic and safety profile of GW433908 across the age range studied, identify an appropriate dose for use in HIV-infected pediatric patients, and evaluate the activity of this dose (or doses) in treatment. Studies that do not define the therapeutic dose in pediatric patients in all studied age groups will be interpreted by the Division/FDA as non-responsive to this Written Request.

Statistical information, including power of study and statistical assessments:

Descriptive analyses of multiple-dose pharmacokinetic, safety and activity data of GW433908 in combination with low-dose RTV in HIV-infected pediatric patients four weeks to 17 years old should be provided. Descriptive analyses of multiple-dose pharmacokinetics of GW433908 (without RTV) in HIV-infected pediatric patients ~~four weeks~~ two to five years old should also be provided. 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.

Four weeks to < six months: 8 patients
Six months to < two years: 6 patients
Two years to < six years: 12 patients
Six years to < 12 years: 8 patients
12 years to < 17 years: 6 patients

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

Reports of the studies that meet the terms of the Written Request dated December 26, 2001, as amended by this letter and by previous amendments dated January 10, 2003, June 19, 2003, August 14, 2006 and December 23, 2009, must be submitted to the Agency on or before October 31, 2011, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

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 (240-276-9327) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 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:

- In accordance with section 505A(e)(2), 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 indicating you have not marketed the new pediatric formulation.

- Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that fosamprenavir calcium 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, FDA 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:

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

- 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.

If you have any questions, call Stacey Min, Pharm.D., Regulatory Project Manager, at (301) 796-4253.

Sincerely,

{See appended electronic signature page}

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

Attachment (Complete Clean Copy of Written Request as amended)

Reference is being made to your correspondence dated November 22, 2010, requesting changes to FDA's December 26, 2001, Written Request as amended on January 10, 2003, June 19, 2003, August 14, 2006 and December 23, 2009 for LEXIVA® (fosamprenavir calcium).

To obtain needed pediatric information on LEXIVA® (fosamprenavir calcium), 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 Written Request supersedes all earlier versions.

Type of studies:

Multiple-dose pharmacokinetic and safety study of GW433908 in combination with low-dose ritonavir (RTV) in HIV-infected pediatric patients 4 weeks to 17 years old. Multiple-dose pharmacokinetic assessment of GW433908 (without RTV) to determine a recommended dose in HIV-infected pediatric patients 2 to 5 years old.

The objective of these studies will be to determine the pharmacokinetic and safety profile of GW433908 across the age range studied, identify an appropriate dose for use in HIV-infected pediatric patients, and evaluate the activity of this dose (or doses) in treatment. Studies that do not define the therapeutic dose in pediatric patients in all studied age groups will be interpreted by the Division/FDA as non-responsive to this Written Request.

Indication to be studied:

Treatment of HIV infection in pediatric patients.

Age group in which studies will be performed:

HIV infected pediatric patients from four weeks to adolescence.

Drug Information:

Dosage form: 700 mg tablets and 50 mg/mL oral suspension.

The studies described above should use an age-appropriate formulation of GW433908**.** The relative bioavailability of this formulation should be determined and compared with the marketed formulation of GW433908. 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:

- Rash, including Stevens-Johnson syndrome
- Gastrointestinal symptoms
- Elevated liver transaminase levels
- Elevated trigylcerides
- Metabolic disorders such as hyperglycemia, hyperlipidemia, abnormal fat redistribution.

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

The safety of GW433908 must be studied in an adequate number of pediatric patients to characterize adverse events across the age range.

Statistical information, including power of study and statistical assessments:

Descriptive analyses of multiple-dose pharmacokinetic, safety and activity data of GW433908 in combination with low-dose RTV in HIV-infected pediatric patients four weeks to 17 years old should be provided. Descriptive analyses of multiple-dose pharmacokinetics of GW433908 (without RTV) in HIV-infected pediatric patients two to five years old should also be provided. 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.

Four weeks to < six months: 8 patients
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12 years to < 17 years: 6 patients

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

Pharmacokinetic parameters such as: Cmax, Cmin, Tmax, t ½, AUC, and apparent oral clearance

Safety and tolerability

HIV-infected pediatric patients should be followed for safety for a minimum of six months at the recommended dose of GW433908 administered in combination with RTV. In addition, please also

submit plans for long-term safety monitoring in HIV-infected pediatric patients who have received GW433908.

Safety data should be collected on approximately 100 patients.

Activity

Assessment of changes in plasma HIV RNA levels and in CD4 cell counts (in HIV-infected pediatric patients)

Resistance

Collect and submit information regarding the resistance profile (genotypic and phenotypic) of clinical isolates at baseline and during treatment from pediatric patients receiving GW433908, particularly from those who experience loss of virologic response.

Labeling that may result from the study(ies):

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

Format of reports to be submitted:

Full or interim 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.

Timeframe for submitting reports of the studies:

Reports of the above studies through 24 weeks must be submitted to the Agency on or before October 31, 2011. 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 (NDA) 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 (240-276-9327) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773.

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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:

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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.

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

/s/

EDWARD M COX
02/04/2011