

FILED IN 4711 McKay

JUL 16 1999

IND 53,971

Triangle Pharmaceuticals, Inc.
Attention: Anne McKay
4 University Place
4611 University Drive
Durham, NC 27707

Dear Ms. McKay:

Reference is made to your Proposed Pediatric Study Request submitted on June 14, 1999, for emtricitabine to IND 53,971.

To obtain needed pediatric information on emtricitabine, 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:

Type of studies:

Multiple-dose pharmacokinetic, safety and activity study of emtricitabine in combination with other antiretroviral agents in HIV-infected pediatric patients.

Multiple-dose pharmacokinetic and safety study of emtricitabine in HIV-exposed neonates (born to HIV-infected mothers).

Indication to be studied:

Treatment of HIV infection

Age group in which studies will be performed:

HIV-infected pediatric patients from 1 month to 16 years and HIV-exposed neonates (born to HIV-infected mothers).

Drug Information

Dosage form: tablets and age appropriate-formulation

Route of administration: oral

Regimen: to be determined by development program

Drug specific safety concerns:

There is limited information on emtricitabine in humans. Early clinical trials have identified headache, dizziness, nausea, CNS effects, and rash, as possible adverse events related to FTC.

Statistical information, including power of study and statistical assessments:

Descriptive analyses of multiple-dose pharmacokinetic, safety and activity data in HIV-infected pediatric patients.

Descriptive analyses of multiple-dose pharmacokinetic and safety data in HIV-exposed neonates (born to HIV-infected mothers).

Studies should include an adequate number of patients to characterize pharmacokinetics over the age range studied, taking into account inter-subject and intra-subject variability. The number of subjects should be uniformly distributed across the age range studied.

Clinical endpoints including primary efficacy endpoints:

Pharmacokinetics

Parameters such as C_{max} , C_{min} , T_{max} , $t_{1/2}$, AUC

Safety and tolerability

HIV-infected pediatric patients should be followed for safety for a minimum of six months. HIV-exposed neonates (born to HIV-infected mothers) should have safety assessments, on or off treatment (as appropriate), for a minimum of six months after start of therapy. In addition, please also submit plans for long-term safety monitoring in HIV-exposed neonates and HIV-infected pediatric patients who have received emtricitabine.

Activity

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

Labeling that may result from the study (ies):

Information regarding dosing, safety and activity in HIV-infected pediatric population and information regarding dosing and safety in HIV-exposed neonates (born to HIV-infected mothers).

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 July 1, 2001. Please keep in mind that pediatric exclusivity only extends 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.

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. We recommend you seek a written agreement, as described in the guidance to industry (*Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act*), with FDA before developing pediatric protocols. 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.

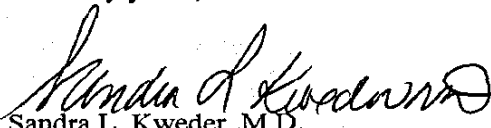
Reports of the studies should be submitted as a supplement to your approved NDA or as a new drug application, as appropriate, with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**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 Written Request, 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 Ms. Christine Kelly, RN, MS, MBA, Regulatory Health Project Manager, at 301-827-2335.

Sincerely yours,



Sandra L. Kweder, M.D.

Acting Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

IND 53,971

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Concurrence:

HFD-5530/MO/Fleischer *6/28/99*

HFD-530/MO Team Leader/Cvetkovich

HFD-530/SCSO/DeCicco *6-28-99*

HFD-530/DD/Birnkrant *MB 6/28/99*

HFD-530/Director/Jolson *HJB 6/28/99*

cc:

Archival IND 53,971

HFD-530/Division file

HFD-530/PM/Kelly

HFD-530/MO Team Leader/Cvetkovich *TC 6/28/99*

HFD-5530/MO/Fleisher

HFD-530/Biopharm/Reynolds/Gillespie

HFD-530/Chem/Miller/Lunn

HFD-104/Acting Office Director/Dr. Kweder

HFD-600/Office of Generic Drugs

HFD-2/MLumpkin

HFD-104/DMurphy

HFD-6/Kroberts

**PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION REQUEST (IR)**