



NDA 22-187/IND 63,646

**REVISED WRITTEN REQUEST
AMENDMENT # 2**

Tibotec, Inc.
Attention: Susan Fiordeliso
Senior Manager, Global Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, N.J 08560

Dear Ms. Fiordeliso:

Please refer to your correspondence dated September 26, 2008, requesting changes to FDA's April 3, 2008, Written Request for pediatric studies for Intelence™ (etravirine).

We have reviewed your proposed changes and are amending the "Statistical information, including power of the study and statistical assessments" section of the Written Request based on new recommendations from the Office of Clinical Pharmacology. Please propose the number of subjects in each age group for PK sampling. Your proposed number(s) must be able to meet the statistical requirements stated in the **'Statistical information, including power of study and statistical assessments'** section of the Written Request. The number of subjects and sampling scheme should be agreed upon with the Division. In addition, we are amending the "Labeling that may result from the studies" section of the Written Request, as listed below. All other terms stated in our Written Request issued on April 3, 2008, and as amended on December 17, 2008, remain the same.

Statistical information, including power of study and statistical assessments

Descriptive analyses of multiple-dose pharmacokinetic, safety and activity data in HIV-1-infected pediatric subjects are required. Studies must include an adequate number of subjects to characterize pharmacokinetics for dose selection. The study must be prospectively powered to target a 95% CI within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution for etravirine in the following age groups:

- 12 months to < 2 years
- 2 years to < 6 years
- 6 years to < 12 years, and
- 12 years to 18 years.

Final selection of sample size for each age group must take into account all potential sources of variability, including inter-subject and intra-subject variability. As study data are evaluated, the

sample size must be increased as necessary for characterization of pharmacokinetics across the intended age range.

Labeling that may result from the studies

You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that etravirine 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). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

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 April 3, 2008, as amended by this letter, must be submitted to the Agency on or before March 13, 2013, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

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. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please 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.

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.

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 to the pediatric population.

If you have any questions, call Carrie Ceresa, Pharm D., MPH, Regulatory Project Manager, at 301-796-4108.

Sincerely,

{See appended electronic signature page}

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

Attachment (Complete Copy of Written Request as amended)

Reference is made to your Proposed Pediatric Studies Request submitted on October 9, 2007, for Intelence™ (etravirine) to IND 63,646 for treatment of HIV-1 infection.

To obtain needed pediatric information on etravirine, 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), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the following studies:

Type of studies:

Multiple-dose pharmacokinetic, safety and activity studies of etravirine, in combination with other antiretroviral agents, in HIV-1-infected, treatment-experienced pediatric patients.

The objective of these studies will be to determine the pharmacokinetic and safety profile of etravirine across the age range studied, identify an appropriate dose (or doses) for use in HIV-1-infected pediatric patients, and evaluate the activity of this dose (or doses) in treatment.

These studies must take into account adequate (e.g., proportionate to study population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

Indication to be studied:

Treatment of HIV-1 infection in treatment-experienced pediatric patients

Age group in which studies will be performed:

HIV-1-infected, treatment-experienced pediatric patients from 1 to 18 years of age

Drug Information

Dosage form: Age-appropriate formulation

Route of administration: Oral

Regimen: To be determined by development program

Use an age-appropriate formulation in the studies described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric populations, you must seek marketing approval for that age appropriate formulation.

If 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric populations studied (i.e., receives marketing approval), 2) the Agency publishes 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 to indicate that the approved pediatric formulation has not been marketed, in accordance with section 505A(e)(2).

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. Under these circumstances, 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 labeling 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 must 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 about your product, provide specific safety parameters that your pediatric program will monitor. Safety monitoring and data collection should include, but not be limited to:

- o Rash, including Stevens-Johnson syndrome
- o Liver enzyme elevations
- o Lipid profiles
- o Coagulation parameters and bleeding events
- o Lipodystrophy

Safety of etravirine must be studied in an adequate number of pediatric patients to characterize adverse events across the age range. A minimum of 100 patients with at least 24-week safety data is required.

Statistical information, including power of study and statistical assessments:

Descriptive analyses of multiple-dose pharmacokinetic, safety and activity data in HIV-1-infected pediatric subjects is required. Studies must include an adequate number of subjects to characterize pharmacokinetics for dose selection. The study must be prospectively powered to target a 95% CI within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution for etravirine in the following age groups:

- 12 months to < 2 years
- 2 years to < 6 years
- 6 years to < 12 years
- 12 years to 18 years

Final selection of sample size for each age group must take into account all potential sources of variability, including inter-subject and intra-subject variability. As study data are evaluated, the

sample size must be increased as necessary for characterization of pharmacokinetics across the intended age range.

Study Endpoints:

Pharmacokinetics: Parameters including C_{max}, C_{min}, T_{max}, t_{1/2}, AUC, apparent systemic clearance and apparent volume of distribution.

Safety and tolerability: HIV-1-infected pediatric patients must be followed for safety for a minimum of six months at the recommended dose or higher. In addition, submit plans for long-term safety monitoring in HIV-1-infected pediatric patients who have received etravirine.

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

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

Labeling that may result from the studies:

You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that etravirine 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). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

Format and types of reports to be submitted:

You must submit full or interim study reports containing at least 24-week data (which have not been previously submitted to the Agency) that address the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies 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, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. These postmarketing adverse event reports should be submitted as narratives and tabular reports.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document “Study Data Specifications,” which is posted on the FDA website at <http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf>

and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at <http://www.fda.gov/cder/guidance/7087rev.htm>.

Timeframe for submitting reports of the studies:

Reports of the above studies must be submitted to the Agency on or before March 30, 2013. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

Response to Written Request:

Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the studies. If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the studies, but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

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. Reports of the studies should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe are 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 to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9310.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, 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 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).

FDA will post the medical, statistical and clinical pharmacology reviews on the FDA website at <http://www.fda.gov/cder/pediatric/index.htm> .

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.

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 are 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 submission of such 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.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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NDA-22187	GI-1	TIBOTEC INC	TMC 125 ETRAVIRINE
IND-63646	GI-1	TIBOTEC INC	TMC125

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
03/10/2010