DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-187

Tibotec, Inc.
Attention: Susan Fiordeliso
Manager, Global Regulatory Affairs
1020 Stony Hill Road, Suite 300
Yardley, PA. 19067

Dear Ms. Fiordeliso:

Please refer to your drug application (NDA) 22-187, submitted as rolling review, dated July 17, 2007, received July 18, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Intelence™ (etravirine) 100 mg tablets.

We acknowledge receipt of your submissions dated:

January 17, 2008	December 3, 2007	September 4, 2007
January 16, 2008	October 30, 2007	July 17, 2007
January 15, 2008	October 24, 2007	July 6, 2007
January 4, 2008	October 4, 2007	June 4, 2007
December 14, 2007	September 7, 2007	

This new drug application provides for the use of Intelence™ (etravirine) 100 mg tablets in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adult patients, who have evidence of viral replication and HIV-1 strains resistant to a non-nucleoside reverse transcriptase inhibitor (NNRTI) and other antiretroviral agents.

NDA 22-187 was not referred to an advisory committee for review because there are several previously approved agents in the non-nucleoside class of drugs, evaluation of the safety data did not reveal particular safety issues that were unexpected for this class, and the design and results of the safety and efficacy trials did not pose particular concerns.

We completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.510), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text (package insert, patient package insert and immediate container label). Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert and patient package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, “SPL for approved NDA22-187.”

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-187**." Approval of this submission by FDA is not required before the labeling is used.

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. We remind you of your post marketing study commitments specified in your submission dated January 17, 2008 was agreed upon during a teleconference held on January 11, 2008. This commitment, along with the agreed-upon completion date, is listed below.

1. Submit study reports for Week 48 data analyses for the ongoing Phase 3 studies TMC125-C206 and TMC125-C216 to support the traditional approval of etravirine.

   Final report submission: January 2009

Submit final study reports to NDA 22-187 as a supplemental application. For administrative purposes, all submissions relating to this postmarketing study commitment must be clearly designated "**Subpart H Postmarketing Study Commitments**."

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for ages birth to 8 weeks and deferring pediatric studies for ages 2 months to 18 years for this application. We are waiving submission of pediatric studies in pediatric subjects from birth up to 8 weeks of age because etravirine is being approved for the treatment of HIV-1 in treatment-experienced patients.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. These commitments are listed below.

2. Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects from 6 years to 18 years of age. Conduct a pediatric safety and activity study of etravirine with activity based on the results of virologic response over at least 24 weeks of dosing and safety monitored over 48 weeks.

   Protocol submission: June 2008
   Final report submissions: June 2010

3. Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects from 2 months to 6 years of age. This study will determine the pharmacokinetic profile, safety, and activity of etravirine in pediatric subjects from 2 months to 6 years of age.

   Protocol submission: June 2010
   Final report submissions: June 2013

Please submit final study reports to this NDA. For administrative purposes, all submissions related to these pediatric postmarketing study commitments must be clearly designated "**Required Pediatric Study Commitments**".

In addition, we note the following postmarketing study commitments, specified in your submission dated January 16, 2008, that were agreed-upon during teleconferences held on January 11, 2008 and January 15, 2008, and are not a condition of the accelerated approval. These commitments are listed below:

Clinical:

4. Conduct a study of etravirine in treatment-experienced female patients to elucidate any potential gender differences in efficacy and safety.

   Protocol Submission: Completed, cross referenced to IND 62,477 for TMC114 (PREZISTA); "*Gender, Race And Clinical Experience (GRACE)*" trial, TMC114HIV3004
   Final Report Submission: December 2009 (TMC125 subgroup analysis report of TMC114HIV3004)

5. Conduct a 48-week clinical study of treatment-experienced patients enrolling at least 200 subjects to evaluate safety and pharmacokinetics of etravirine when given with drug combinations that do not contain darunavir/rtv. Submit an interim report including analyses of 12-week safety data and supportive efficacy data with the Safety Update submission for the traditional approval supplemental new drug application for etravirine.

   Protocol submission: July 2008
   Final study report submission: July 2011

Pharmacology Toxicology:

6. Complete ongoing carcinogenicity study in mice and submit the final report.

   Protocol submission date: Completed
   Final study report submission date: January 2009

7. Complete ongoing carcinogenicity study in rats and submit the final report.

   Protocol submission date: Completed
   Final study report submission date: January 2009

Clinical Pharmacology:

8. Conduct an *in vivo* drug-drug interaction study between etravirine and fluconazole.

   Protocol submission date: by July 2008
   Final study report submission date: by August 2009

9. Conduct an *in vivo* drug-drug interaction study between etravirine and buprenorphine/naloxone.

   Protocol submission date: by July 2008
   Final study report submission date: by August 2010

Please submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

The following are not postmarketing study commitments; however, we note that they are specified in your submission of January 17, 2008 and were agreed-upon in a teleconference held on January 11, 2008 and in electronic mail correspondence on January 17, 2008; these are listed below:

1. Please assess the combination antiviral activity relationships of etravirine with maraviroc and with raltegravir.

   Final Study report submission date: by December 2008

2. Please submit a final study report for the Expanded Access Program, conducted under IND 75084, within 8 months of close of study.

As required by 21 CFR 314.550, submit all promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement. Send two copies of all promotional materials directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Anne Marie Russell, Ph.D., Regulatory Project Manager, at (301) 796-2014.

Sincerely,

{See appended electronic signature page}

Edward Cox, M.D., M.P.H.
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

Enclosures: Approved draft package insert (PI), patient package insert (PPI), and immediate container label .

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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