DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-976

Tibotec, Inc.
Attention: Jenny Z. Lin, PharmD
Manager, Global Regulatory Affairs
1020 Stony Hill Road, Suite 300
Yardley, PA 19067

Dear Dr. Lin:

Please refer to your new drug application (NDA) dated December 22, 2005, received December 23, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PREZISTA (darunavir) tablets, 300 mg.

We acknowledge receipt of your submissions dated:

September 23, 2005	February 27, 2006	June 12, 2006
November 4, 2005	March 21, 2006	June 19, 2006
November 17, 2005	March 29, 2006	June 21, 2006
December 22, 2005	April 14, 2006	June 22, 2006
February 9, 2006	June 1, 2006	

This new drug application provides for the use of PREZISTA™ (darunavir) tablets, co-administered with 100 mg of ritonavir, for the treatment of human immunodeficiency virus (HIV) infection in antiretroviral treatment-experienced adult patients, such as those with HIV-1 strains resistant to more than one protease inhibitor.

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 labeling text and patient labeling. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

The final printed labeling (FPL) must be identical to the agreed upon enclosed labeling (text for the package insert and patient package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL, as soon as it is available but no more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material.

For administrative purposes, designate this submission "**FPL for approved NDA 21-976**." Approval of this submission by FDA is not required before the labeling is used.

Submit content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

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 postmarketing study commitments specified in your submission dated June 22, 2006. These commitments, along with any completion dates agreed upon, are listed below.

1. By December 31, 2007, submit the final study reports and datasets of the 96-week data for the ongoing Phase 2b studies TMC114-C202, TMC114-C213, TMC 114-C208, and TMC114-C215.

2. By December 31, 2007, submit the final study reports and datasets of the 48 week data for the ongoing Phase 3 studies TMC114-C211 and TMC114-C214.

Please submit final study reports to NDA 21-976 as supplemental applications. For administrative purposes, all submissions relating to these postmarketing study commitments must be clearly designated "**Subpart H Postmarketing Study Commitments**."

Furthermore, 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 deferring submission of your pediatric studies for ages 6 to 17 years until June 30, 2008. Also, we are deferring submission of your pediatric studies for less than 6 years of age until June 30, 2011.

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.

3. Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric patients ages 6 to 17 years. Please assess the pharmacokinetics, safety, tolerability and antiviral activity of two alternative doses of a suitable pediatric formulation in combination with ritonavir, in treatment-experienced pediatric children and adolescents between 6 and 17 years of age.

Protocol Submission:	Completed
Final Report Submission:	24 week data by June 30, 2008

4. Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric patients less than 6 years of age. Please evaluate dose requirements and safety in pediatric patients less than 6 years of age with HIV-1 infection after preliminary review of data from the 6 to 17 year olds in trial TMC114-C212 with the Division of Antiviral Products (DAVP).

    Protocol Submission: by December 31, 2008
    Final Report Submission: by June 30, 2011

Submit final study reports to this NDA. For administrative purposes, all submissions related to this/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 June 22, 2006, that are not a condition of the accelerated approval. These commitments are listed below:

Drug-Drug Interaction Trials

5. Conduct an *in vivo* drug-drug interaction study between darunavir/rtv b.i.d. and rifabutin.

    Protocol Submission: by July 31, 2006
    Final Report Submission: by June 30, 2007

6. Conduct an *in vivo* drug-drug interaction study between darunavir/rtv b.i.d. and buprenorphine/naloxone.

    Protocol Submission: by December 31, 2006
    Final Report Submission: by January 31, 2008

7. Conduct an *in vivo* drug-drug interaction study between darunavir/rtv b.i.d. and carbamazepine.

    Protocol Submission: by December 31, 2006
    Final Report Submission: by January 31, 2008

Pharmacology/Toxicology

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

    Protocol Submission: Completed
    Final Report Submission: by December 31, 2007

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

    Protocol Submission: Completed
    Final Report Submission: by December 31, 2007

Pharmacokinetics

10. Please conduct a cocktail study to determine the effects of steady state darunavir/rtv 600/100 mg b.i.d. on the metabolism of CYP450 probe substrates for the following enzymes: CYP2C9, CYP2C19, and CYP2D6.

    Protocol Submission: by December 31, 2006
    Final Report Submission: by January 31, 2008

Special Populations

11. Evaluate the pharmacokinetics of darunavir/rtv in HIV-negative subjects with Child-Pugh A and Child-Pugh B liver disease in order to determine dosing recommendations.

    Protocol Submission: by July 31, 2006
    Final Report Submission: by March 31, 2007

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

    Protocol Submission: by December 31, 2006
    Final Report Submission: 24 week data by December 31, 2008

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 request the following information be submitted:

Drug-Drug Interaction Trials

1. Please submit the results from your planned study TMC114-C127, a drug-drug interaction study between darunavir/rtv b.i.d. and methadone.

Clinical

2. In addition to the required periodic adverse drug experience reports [21 CFR 314.80(c)(2)], please submit a separate periodic adverse drug experience report for rash.

Microbiology

3. Determine response rates based upon presence of specific cleavage site mutations at baseline and submit this analysis with the PREZISTA traditional approval application.

4. Determine the protease cleavage site mutations that occur most frequently (>10%) in virologic failure isolates and submit this analysis with the PREZISTA traditional approval application.

5. Determine if the most frequently occurring protease cleavage site mutations contributed to decreases in darunavir susceptibility through site-directed mutagenesis and submit this analysis with the PREZISTA traditional approval application.

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
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

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.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.