DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-976/S-006

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

Dear Ms. Fiordeliso:

Please refer to your supplemental new drug application dated December 20, 2007, received December 21, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for PREZISTA (darunavir) 300 mg and 600 mg tablets.

We acknowledge receipt of your submissions dated February 28, 2008, March 28, 2008, April 18, 2008, April 30, 2008, May 14, 2008, June 13, 2008, June 17, 2008, July 2, 2008, July 21, 2008, September 4, 2008 and October 8, 2008.

This supplemental 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) in antiretroviral treatment-experienced adult patients.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and patient labeling. We approved this NDA (21-976/000) under the 21 CFR 314 Subpart H regulations for accelerated approval of new drugs for serious or life-threatening illnesses. Approval of this supplement and NDA 21-976, supplement 007, fulfills your commitments made under 21 CFR 314.510, listed as PMCs 1 and 2 in the June 23, 2006, approval letter:

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.

Approval of this supplement also fulfills the following postmarketing commitments as numbered in the June 23, 2006, approval letter. These commitments are listed below:

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

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

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

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

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.

The following postmarketing commitment acknowledged in our June 23, 2006, approval letter has not been completed:

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

We acknowledge receipt of your submission of June 25, 2008, in support of fulfillment of the following postmarketing commitment listed in our June 23, 2006, approval letter:

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

The submission of June 25, 2008 is currently under review.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to below 3 years of age because of evidence strongly suggesting the drug would be unsafe in this pediatric age group. This decision is based on the results of juvenile rat toxicology studies that provide evidence of a potential safety risk as a result of drug-brain accumulation.

Your deferred pediatric studies required by section 505B(a) of the Federal Food and Drug and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. We remind you of the deferred pediatric studies as identified in the June 23, 2006, approval letter for NDA 21-976/000.

We acknowledge receipt of your submission of June 20, 2008 in support of fulfillment of

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: June 20, 2008

The submission of June 20, 2008 is currently under review.

Because we are waiving the pediatric study requirement for ages 0 to below 3 years of age, you are released from postmarketing requirement number 4, acknowledged in our June 23, 2006, approval letter:

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

Postmarketing requirement 4 is now replaced with the following required deferred pediatric study:

1. Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric patients 3 to 6 years of age. Please evaluate dose requirements and safety in treatment-experienced pediatric patients 3 to 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 required pediatric postmarketing study must be clearly designated "**Required Pediatric Assessment(s)".**

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

Since PREZISTA was approved in June 2006, for the treatment of human immunodeficiency virus (HIV) infection in antiretroviral treatment-experienced adult patients, we have reviewed new data from

submitted to FDA from other juvenile toxicology studies. Mortality was observed across all dose groups in the study of juvenile rats directly dosed at post-natal days (PDN) 5, 8 and 11, as well as juvenile rats directly dosed on PND 12. As a result of these findings, we also re-analyzed data from reproductive toxicology studies. These re-analyses raise a safety concern about the use of PREZISTA in pregnant women and neonates. These re-analyses were not available when PREZISTA was granted marketing authorization for the treatment of HIV infection in antiretroviral treatment-experienced adult patients. Therefore, we consider this information to be "new safety information" as defined in FDAAA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of serious risk, that is, increased mortality and reproductive toxicity in animal studies that may be relevant to pregnant women and neonates.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, we have determined that you are required, pursuant to section 505(o) (3) of the FDCA, to conduct the following study:

2. Perform a nonclincal reproductive toxicology study in a relevant species which achieves an adequate AUC exposure margin (compared to human serum exposure) in order to establish the safety profile of darunavir in utero. Submit your protocol for review prior to initiation of the reproductive toxicology study.

The timetable you submitted on October 21, 2008, states that you will conduct this study according to the following schedule:

Protocol Submission:	September, 2009
Final Report Submission:	April, 2011

Submit the protocol to your IND 62,477, with a cross-reference letter to this NDA 21-976. Submit all final reports to your NDA 21-976. Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing study requirement as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2(vii). We remind you that to

comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

CONTENT OF LABELING

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(1)] 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 text for the 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 NDA 21-976/S-006."**

In addition, within 21 days of the date of this letter, amend any pending applications for this NDA with content of labeling in structures product labeling (SPL) format to include the changes approved in this application.

Marketing the product with FPL that is not identical to the approved labeling text and in the required format may render the product misbranded and an unapproved new drug.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Antiviral Products and two copies of both the promotional materials and the package insert 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

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

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.