DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-814

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Nancy L. McKay, P.E.
Senior Associate Director, Drug Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368

Dear Ms. McKay:

Please refer to your new drug application (NDA) 21-814 dated December 21, 2004, received December 22, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aptivus® (tipranavir) capsules, 250 mg.

We acknowledge receipt of your submissions dated:

Dec. 29, 2004	Feb. 25. 2005	Apr. 06, 2005	May 10, 2005 (2)
Jan. 04, 2005	Feb. 28. 2005 (2)	Apr. 07, 2005	May 11, 2005
Jan. 12, 2005	Mar. 03, 2005	Apr. 08, 2005	May 13, 2005 (2)
Jan. 13, 2005	Mar. 04, 2005	Apr. 11, 2005	May 16, 2005
Jan. 25, 2005 (2)	Mar. 15, 2005 (3)	Apr. 12, 2005 (2)	May 21, 2005
Feb. 02, 2005	Mar. 16, 2005	Apr. 15, 2005 (2)	May 27, 2005
Feb. 03, 2005	Mar. 17, 2005	Apr. 19, 2005 (4)	Jun. 03, 2005
Feb. 09, 2005	Mar. 21, 2005	Apr. 21, 2005	Jun. 07, 2005
Feb. 10, 2005 (2)	Mar. 24, 2005	Apr. 28, 2005	Jun. 10, 2005 (2)
Feb. 16, 2005	Mar. 25. 2005 (2)	Apr. 29, 2005 (2)	Jun. 17, 2005
Feb. 22, 2005	Mar. 31, 2005	May 02, 2005	Jun. 21, 2005 (2)
Feb. 23, 2005	Apr. 04, 2005 (2)	May 05, 2005	

This new drug application provides for the use of Aptivus® (tipranavir) capsules, 250 mg, co-administered with 200 mg of ritonavir, for combination antiretroviral treatment of HIV-1 infected adult patients with evidence of viral replication, who are highly treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors.

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 required 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 enclosed labeling (text for the package insert, text for the patient package insert, and immediate container label). 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 an electronic version of the FPL 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. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-814**." 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 postmarketing study commitments specified in your submission dated June 21, 2005. These commitments, along with any completion dates agreed upon, are listed below.

1. By September 30, 2006, please submit the study reports for the 48 week data of the ongoing Phase 3 study RESIST-1 (1182.12).

2. By September 30, 2006, please submit the study reports for the 48 week data of the ongoing Phase 3 study RESIST-2 (1182.48).

Please submit final study reports to NDA 21-814 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 2 weeks to 2 years until January 31, 2009. Also, we are deferring submission of your pediatric studies for ages 2 years to18 years until June 30, 2006.

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. Assess pharmacokinetics, safety and antiviral activity in two alternative doses of either tipranavir/ritonavir liquid formulation or capsules in addition to safety, in antiretroviral naive and experienced children and adolescents between 2 and 18 years of age.

   Protocol Submission: Completed
   Final Report Submission: June 30, 2006

4. Evaluate dose requirements and safety in pediatric patients age 2 weeks to 2 years with HIV-1 infection after review of 48 week data from the 2 to 18 year old children in trial 1182.14 with the Division of Antiviral Drug Products (DAVDP).

Protocol Submission: September 30, 2006
Final Report Submission: January 31, 2009

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 your postmarketing study commitments that were specified in your submission dated June 21, 2005 and are not a condition of the accelerated approval. These commitments are listed below:

Drug-Drug Interaction Trials

5. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and atazanavir.

   Final Report Submission: Submitted by December 31, 2005

6. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and buprenorphine/naloxone.

   Protocol Submission: July 15, 2005.
   Final Report Submission: Submitted by June 30, 2006

7. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and carbamazepine.

   Protocol Submission: July 15, 2005
   Final Report Submission: Submitted by September 30, 2006

8. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and tadalafil.

   Protocol Submission: August 31, 2005
   Final Report Submission: Submitted by December 31, 2006

9. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and ribavirin/pegylated IFN alpha 2a.

   Protocol Submission: August 31, 2005.
   Final Report Submission: Submitted by June 30, 2007

10. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and methadone.

    Final Report Submission: Submitted by September 30, 2005

Pharmacology/Toxicology

11. Complete ongoing carcinogenicity study in mice and submit final report.

Protocol Submission: Completed
Final Report Submission: December 31, 2006

12. Complete ongoing carcinogenicity study in rats and submit final report.

Protocol Submission: Completed
Final Report submission: December 31, 2005

Special Populations

13. Assess the long term (48 week) antiviral efficacy and safety of tipranavir/ritonavir in ARV treatment naive patients through the conduct of study 1182.33.

Protocol Submission: Completed
Final Report Submission: September 30, 2006

Evaluate drug resistance in viruses from patients with virologic rebound on initial ART (in 1182.33); please submit data in resistance template.

Protocol Submission: Completed
Final Report Submission: September 30, 2006

Assess metabolic changes being studied in a sub-study of 1182.33.

Protocol Submission: Completed
Final Report Submission: September 30, 2006

14. Conduct a 48-week prospective observational diversity cohort study with tipranavir/ritonavir twice daily stratified by race and gender in HIV-positive patients to assess efficacy and safety, including potential risk parameters such as CD4+ cell count.

Protocol Submission: March 30, 2006
Final Report Submission: September 1, 2008

15. Conduct a 48-week prospective observational cohort study with tipranavir/ritonavir twice daily in patients co-infected with HIV and HBV or HCV to assess efficacy and safety. BI will discuss potential therapeutic drug monitoring substudy for this protocol with the FDA.

Protocol Submission: March 30, 2006
Final Report Submission: July 1, 2008

16. Assess tipranavir/ritonavir pharmacokinetics in HIV-negative subjects with Child-Pugh B liver disease.

Protocol Submission: December 31, 2006
Final Report Submission: December 31, 2007

Pharmacokinetics

17. Conduct a CYP/P-gp mechanistic study to determine effect of tipranavir/ritonavir on individual CYPs.

    Protocol Submission: September 30, 2005
    Final Report Submission: December 31, 2006

Clinical

18. Conduct a formal QT prolongation study.

    Protocol Submission: Special Protocol Assessment Complete
    Final report Submission: June 30, 2006

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, but in your letter dated June 21, 2005, you agreed to:

Drug-Drug Interaction Trials

1. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and bupropion.

2. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and the investigational antiviral drug (b)(4)

3. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and the investigationa1 antiviral drug (b)(4)

4. Conduct a human drug-drug i(b)(4) onavir twice daily and the investigational antiviral drug (b)(4)

5. Conduct a human drug-drug i(b)(4) tipranavir/ritonavir twice daily and the investigational antiviral drug (b)(4)

6. Conduct a human drug-drug interaction study of tipranavir/ritonavir twice daily and the investigational antiviral drug (b)(4)

Pharmacokinetics

7. Conduct a study to assess intracellular triphosphate levels of zidovudine and abacavir when co-administered with tipranavir/ritonavir twice daily.

Clinical

8. Conduct a long-term cardiovascular safety evaluation of Protease Inhibitor/ritonavir (including tipranavir) from epidemiologic databases.

Microbiology

9. Evaluate cleavage site mutations in rebound samples on tipranavir.

Therapeutic Drug Monitoring

10. You agree to meet with DAVDP and the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) within 6 months and develop a pilot study to assess the utility of therapeutic drug monitoring in HIV-infected patients receiving tipranavir/ritonavir. The study will be conducted and the results will be used to either include individualized dosing strategies in the tipranavir label or to assess the value of conducting a larger trial to evaluate the clinical benefit of therapeutic drug monitoring for tipranavir.

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:

Division of Drug Marketing, Advertising and Communications, HFD-042
Food and Drug Administration
5600 Fishers Lane
Rockville MD 20857

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.

If you have any questions, please contact Tanima Sinha, M.S., Regulatory Project Manager, at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

Mark Goldberger, M.D., M.P.H.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration

Attachment: approved draft labeling and patient package insert

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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
6/22/05 05:30:09 PM
for Mark J. Goldberger, MD, MPH