DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21814/S-013
NDA 22292/S-06

SUPPLEMENT APPROVAL

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Maria Gigliotti, M.S.
Associate Director, Drug Regulatory Affairs
900 Ridgebury Rd
P.O. Box 368
Ridgefield, CT 06877

Dear Ms. Gigliotti:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received November 16, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Aptivus® (tipranavir) Capsules (NDA 21814) and Oral Solution, 100mg/mL (NDA 22292).

We acknowledge receipt of your amendments dated January 23, 2012 in response to our additional non-safety labeling change request sent on December 14, 2011 via e-mail.

We also refer to our letter dated October 19, 2011, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for antiretroviral products. This information pertains to the risk of the autoimmune disorder as syndromes that can occur in the setting of immune reconstitution with the use of antiretroviral products.

In addition, we refer to non-safety labeling changes in our October 19, 2011 letter for all antiretroviral products based on recent studies demonstrating decreased transmission of HIV when HIV-infected patients or their uninfected partners take antiretroviral medication.

These supplemental new drug applications provide for revisions to the labeling for Aptivus® (tipranavir) Capsules (NDA 21814) and Oral Solution, 100mg/mL (NDA 22292), consistent with our October 19, 2011 letter and December 14, 2011 e-mail request, as follows (additions are noted by underline and deletions are noted by ~~strikethrough~~).

1. The **RECENT MAJOR CHANGES** in the Highlights section of the label has been added as follows:

----------RECENT MAJOR CHANGES----------

~~Dosage and Administration (2) 5/2010~~
~~Contraindications, Drug Interactions (4.2) 4/2010~~

~~Warnings and Precautions, Drug Interactions (5.3) 4/2010~~

Warnings and Precautions
Immune Reconstitution Syndrome (5.9) X/XXXX

2. The revision date has been changed from 4/2011 to x/2011 at the end of the **HIGHLIGHTS** section and the last page of the label.

3. The **WARNINGS AND PRECAUTIONS/Immune Reconstitution Syndrome** sub-section has been revised as follows:

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including APTIVUS. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

4. The following portion of the Table 4 in the DRUG INTERACTION/7.2 Potential for APTIVUS/ritonavir to Affect Other Drugs sub- section has been revised as follows:

Table 4 Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May be Recommended Based on Drug Interaction Studies or Predicted Interaction

Concomitant Drug Class: Drug name	Effect on Concentration of Concomitant Drug	Clinical Comment
HMG-CoA Reductase Inhibitors:		
Atorvastatin Rosuvastatin	↑ Atorvastatin ↓ Hydroxy-atorvastatin metabolites ~~↑ Tipranavir~~ ↑ Rosuvastatin	~~Use the lowest possible dose of atorvastatin or rosuvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin when in concomitant use of APTIVUS, co-administered with 200 mg of ritonavir.~~ Avoid co-administration with atorvastatin.

5. The Table 7 in the **CLINICAL PHARMACOLOGY/Pharmacokinetics** sub-section has been revised as follows:

Table 7 Drug Interactions: Pharmacokinetic Parameters for Tipranavir in the Presence of Co-administered Drugs

Co-administered Drug	Co-administered Drug Dose (Schedule)	tipranavir/ ritonavir Drug Dose (Schedule)	n	PK	Ratio (90% Confidence Interval) of Tipranavir Pharmacokinetic Parameters with/without Co-administered Drug; No Effect = 1.00		
					C_{max}	**AUC**	**C_{min}**
Rosuvastatin	10 mg (1 dose)	500/200 mg BID (24 dDoses)	16	↔	1.08 (1.00, 1.17)	1.06 (0.97, 1.15)	0.99 (0.88, 1.11)

6. The second paragraph under the second bullet in the **PATIENT COUNSELING INFORMATION/Administration** sub-section has been revised as follows:

~~Patients should be informed that APTIVUS is not a cure for HIV-1 infection and that they may continue to develop opportunistic infections and other complications associated with HIV-1 disease. The long-term effects of APTIVUS are unknown at this time. Patients should be told that there are currently no data demonstrating that therapy with APTIVUS can reduce the risk of transmitting HIV-1 to others through sexual contact.~~ APTIVUS is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using APTIVUS.

Patients should be advised to avoid doing things that can spread HIV-1 infection to others.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom ~~or other barrier method~~ to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** We do not know if APTIVUS can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

7. The end of package insert has been revised as follows:

OT2000~~ND~~OJ282011~~OT2000NC062011~~
10003515/~~X~~x

8. **Patient Information**:

a. The "**Does APTIVUS cure HIV or AIDS?**" section has been revised as follows:

~~**APTIVUS does not cure HIV infection or AIDS.** The long-term effects of APTIVUS are not known at this time. People taking APTIVUS may still get infections or other conditions common in people with HIV (opportunistic infections). It is very important that you stay under the care of your doctor during treatment with APTIVUS.~~

~~**Does APTIVUS lower the chance of passing HIV to other people?**~~

~~APTIVUS does not reduce the chance of passing HIV to others through sexual contact, sharing needles, or being exposed to your blood. Continue to practice safer sex. Use a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions or blood. Never use or share dirty needles.~~

~~Ask your healthcare professional if you have any questions about safer sex or how to prevent passing HIV to other people.~~

APTIVUS does not cure HIV infection or AIDS and you may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. You should remain under the care of a doctor when using APTIVUS.

Avoid doing things that can spread HIV-1 infection.

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom ~~or other barrier method~~ to lower the chance of sexual contact with semen, vaginal secretions, or blood.

b. The fourth bullet in the "**Who should not take APTIVUS?/Do not take APTIVUS if you:"** sub-section has been revised as follows:

- take any of the following types of medicines because **you could have serious side effects:**
    - Migraine headache medicines called "ergot alkaloids". If you take migraine headache medicines, ask your healthcare professional or pharmacist if any of them are "ergot alkaloids".
    - Halcion® (triazolam)
    - Orap® (pimozide)
    - Propulsid® (cisapride)
    - Versed® (midazolam) taken orally
    - Pacenone® (amiodarone)
    - Vascor® (bepridil)
    - Tambocor® (flecainide)
    - Rythmol® (propafenone)
    - Quinaglute dura® (quinidine)

- Zocor® (simvastatin)
- Mevacor® (lovastatin)
- Uroxatral® (alfuzosin)
- Revatio® (sildenafil) for treatment of pulmonary arterial hypertension
- Lipitor® (atorvastatin)

c. The sixth bulleted paragraph in the "**What should I tell my healthcare professional before I take APTIVUS?/Tell your healthcare professional about all of your medical conditions, including if you:**" sub-section has been revised as follows:

- **are breast-feeding. Do not breastfeed.** It is not known if APTIVUS can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk. ~~Do not breast-feed if you are taking APTIVUS. You should not breast-feed if you have HIV because of the chance of passing the HIV virus to your baby. Talk with your healthcare professional about the best way to feed your baby.~~

d. The end of patient package insert has been revised as follows:

Copyright 2011~~1~~2Boehringer Ingelheim International GmbH
ALL RIGHTS RESERVED

OT2000OJ282011~~OT2000NC062011~~
10003515/~~X~~x

Revised: x~~April~~ 2011

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at

http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

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

If you have any questions, call Kyong Hyon, Safety Regulatory Project Manager, at (301) 796-0734.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Deputy Director for Safety
Division of Antiviral Products
Office Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KENDALL A MARCUS
02/17/2012