Subject: Important Safety Information: Intracranial Hemorrhage in Patients Receiving Aptivus® (tipranavir) capsules

Boehringer Ingelheim
Pharmaceuticals, Inc.

Dear Healthcare Professional:

Boehringer Ingelheim is writing to inform you of important new safety information for **Aptivus®** (tipranavir) capsules, co-administered with ritonavir, 500 mg/200 mg BID.

June 30, 2006

- Boehringer Ingelheim has identified 14 intracranial hemorrhage events (ICH), including 8 fatalities, in 13 out of 6,840 HIV-1 infected individuals receiving Aptivus® (tipranavir) capsules, as part of combination antiretroviral therapy, in clinical trials.
- Many of the patients experiencing ICH in the APTIVUS clinical development program had other medical conditions (CNS lesions, head trauma, recent neurosurgery, coagulopathy, hypertension or alcohol abuse) or were receiving concomitant medications, including anticoagulants and antiplatelet agents, that may have caused or contributed to these events. The median time to onset of an ICH event was 525 days on APTIVUS/ritonavir treatment.
- No pattern of abnormal coagulation parameters has been observed in patients receiving APTIVUS in general, or preceding the development of ICH. Therefore, routine measurement of coagulation parameters is not currently indicated in the management of patients on APTIVUS.
- In *in vitro* experiments, tipranavir was observed to inhibit human platelet aggregation at levels consistent with exposures observed in patients receiving APTIVUS/ritonavir.
- In preclinical studies in rodents, APTIVUS treatment induced changes in coagulation parameters (increased prothrombin and activated partial thromboplastin times). At higher doses and in extreme cases, these changes led to bleeding in multiple organs and death. The mechanism for this effect is unknown. This effect was not seen in preclinical studies with dogs.
- APTIVUS/ritonavir should be used with caution in patients who may be at risk for increased bleeding from trauma, surgery or other medical conditions, or who are receiving medications known to increase the risk of bleeding such as antiplatelet agents or anticoagulants.
- An increased risk of ICH has previously been observed in patients with advanced HIV-1 disease / AIDS. Further investigations are ongoing to assess the role of APTIVUS in ICH.

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Information on ICH risk and platelet aggregation inhibition findings will be included in the following sections of the Package Insert:

- Boxed Warnings
- Indications and Usage
- Warnings
- Precautions – Information for Patients
- Adverse Reactions
- Animal Pharmacology / Toxicology (new section)

WARNINGS

(new boxed warning paragraph)

APTIVUS CO-ADMINISTERED WITH 200 MG RITONAVIR HAS BEEN ASSOCIATED WITH REPORTS OF BOTH FATAL AND NON-FATAL INTRACRANIAL HEMORRHAGE. (SEE WARNINGS)

APTIVUS CO-ADMINISTERED WITH 200 MG RITONAVIR HAS BEEN ASSOCIATED WITH REPORTS OF CLINICAL HEPATITIS AND HEPATIC DECOMPENSATION INCLUDING SOME FATALITIES. EXTRA VIGILANCE IS WARRANTED IN PATIENTS WITH CHRONIC HEPATITIS B OR HEPATITIS C CO-INFECTION, AS THESE PATIENTS HAVE AN INCREASED RISK OF HEPATOTOXICITY. (SEE WARNINGS)

INDICATIONS AND USAGE (new usage bullet)

- Use caution when prescribing APTIVUS/ritonavir in patients who may be at risk of increased bleeding or who are receiving medications known to increase the risk of bleeding. **(see WARNINGS)**

WARNINGS

Intracranial Hemorrhage

APTIVUS, co-administered with 200 mg of ritonavir, has been associated with reports of both fatal and non-fatal intracranial hemorrhage (ICH). Many of these patients had other medical conditions or were receiving concomitant medications that may have caused or contributed to these events. No pattern of abnormal coagulation parameters has been observed in patients in general, or preceding the development of ICH. Therefore, routine measurement of coagulation parameters is not currently indicated in the management of patients on APTIVUS.

Platelet Aggregation Inhibition

In *in vitro* experiments, tipranavir was observed to inhibit human platelet aggregation at levels consistent with exposures observed in patients receiving APTIVUS/ritonavir.

APTIVUS/ritonavir should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other medical conditions, or who are receiving medications known to increase the risk of bleeding such as antiplatelet agents or anticoagulants.

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PRECAUTIONS, Information for Patients

Patients should be informed that APTIVUS co-administered with 200 mg of ritonavir has been associated with reports of both fatal and non-fatal intracranial hemorrhage.

Patients should report any unusual or unexplained bleeding to their physician.

ADVERSE REACTIONS
(added term to Nervous System Disorders)

Intracranial hemorrhage

ANIMAL PHARMACOLOGY AND TOXICOLOGY

In preclinical studies, tipranavir treatment induced changes in coagulation parameters (increased prothrombin and activated partial thromboplastin times) in rodents. At higher doses and in extreme cases, these changes led to bleeding in multiple organs and death. The mechanism for this effect is unknown. This effect was not seen in preclinical studies with dogs.

Please see www.APTIVUS.com for the full revised prescribing information, including boxed warnings.

Physicians with patients taking APTIVUS should encourage their patients not to discontinue APTIVUS or any other medications without first speaking with their doctor to evaluate the appropriate course of therapy for their needs.

You can assist us in monitoring the safety of APTIVUS by reporting adverse reactions to the Boehringer Ingelheim Pharmaceuticals Drug Information Unit at Boehringer Ingelheim Pharmaceuticals, Inc. (800 542-6257, OPTION#4) or to the FDA MedWatch program by telephone at 1-800-332-1088, by FAX at 1-800-332-0178, via www.FDA.gov/medwatch, or by mail to MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20857.

Additional medical information about APTIVUS can be obtained by calling the Drug Information Unit at Boehringer Ingelheim Pharmaceuticals, Inc. (800 542-6257, OPTION#4).

Sincerely,

Kirk V. Shepard, MD
Vice President
Clinical & Scientific Affairs

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INDICATIONS AND USAGE

APTIVUS (tipranavir), co-administered with 200 mg of ritonavir, is indicated 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.

This indication is based on analyses of plasma HIV-1 RNA levels in two controlled studies of APTIVUS/ritonavir of 24 weeks duration. Both studies were conducted in clinically advanced, 3-class antiretroviral (NRTI, NNRTI, PI) treatment-experienced adults with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

The following points should be considered when initiating therapy with APTIVUS/ritonavir:

- The use of other active agents with APTIVUS/ritonavir is associated with a greater likelihood of treatment response (see **CLINICAL PHARMACOLOGY, Microbiology** and **INDICATIONS AND USAGE, Description of Clinical Studies**).
- Genotypic or phenotypic testing and/or treatment history should guide the use of APTIVUS/ritonavir (see **CLINICAL PHARMACOLOGY, Microbiology**). The number of baseline primary protease inhibitor mutations affects the virologic response to APTIVUS/ritonavir (see **CLINICAL PHARMACOLOGY, Microbiology**).
- Use caution when prescribing APTIVUS/ritonavir in patients who may be at risk for increased bleeding or who are receiving medications known to increase the risk of bleeding. **(see WARNINGS)**
- Liver function tests should be performed at initiation of therapy with APTIVUS/ritonavir and monitored frequently throughout the duration of treatment (see **WARNINGS**).
- Use caution when prescribing APTIVUS/ritonavir to patients with elevated transaminases, hepatitis B or C co-infection or other underlying hepatic impairment (see **WARNINGS**).
- The extensive drug-drug interaction potential of APTIVUS/ritonavir when co-administered with multiple classes of drugs must be considered prior to and during APTIVUS/ritonavir use (see **CLINICAL PHARMACOLOGY** and **CONTRAINDICATIONS**).
- The risk-benefit of APTIVUS/ritonavir has not been established in treatment-naïve adult patients or pediatric patients.

There are no study results demonstrating the effect of APTIVUS/ritonavir on clinical progression of HIV-1.

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Important Safety Information for Aptivus® (tipranavir) capsules

• Aptivus® (tipranavir) capsules co-administered with 200 mg ritonavir has been associated with reports of both fatal and non-fatal intracranial hemorrhage

• Use caution when prescribing APTIVUS/ritonavir in patients who may be at risk of increased bleeding or who are receiving medications known to increase the risk of bleeding

• APTIVUS (tipranavir) co-administered with 200 mg ritonavir (APTIVUS/ritonavir) has been associated with reports of clinical hepatitis and hepatic decompensation, including some fatalities. Extra vigilance is warranted in patients with chronic hepatitis B or hepatitis C co-infection, as these patients have an increased risk of hepatotoxicity

• The extensive drug-drug interaction potential of APTIVUS/ritonavir when co-administered with multiple classes of drugs must be considered prior to and during APTIVUS/ritonavir use

• APTIVUS/ritonavir is contraindicated in patients with known hypersensitivity to any of the ingredients of the product

• APTIVUS/ritonavir is contraindicated in patients with moderate to severe (Child-Pugh Class B and C) hepatic insufficiency

• APTIVUS/ritonavir is contraindicated with amiodarone, bepridil, flecainide, propafenone, quinidine, astemizole, terfenadine, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, pimozide, midazolam, or triazolam due to the potential for serious and/or life-threatening events

• APTIVUS must be co-administered with 200 mg of ritonavir to exert its therapeutic effect. Failure to correctly co-administer APTIVUS with ritonavir will result in reduced plasma levels of tipranavir that will be insufficient to achieve the desired antiviral effect and will alter some drug interactions

• Please refer to the complete ritonavir prescribing information for a description of ritonavir contraindications and additional information on precautionary measures

• All patients should be followed closely with clinical and laboratory monitoring, especially those with chronic hepatitis B or C co-infection, as these patients have an increased risk of hepatotoxicity. Liver function tests should be performed prior to initiating and frequently throughout therapy with APTIVUS/ritonavir

• Patients with chronic hepatitis B or hepatitis C co-infection or elevations in transaminases are at approximately 2.5-fold risk for developing further transaminase elevations or hepatic decompensation. Additionally, Grade 3 and 4 increases in hepatic transaminases were observed in 6% of healthy volunteers in Phase 1 studies and 6% of subjects receiving APTIVUS/ritonavir in Phase 3 studies

• Patients with signs or symptoms of clinical hepatitis should discontinue APTIVUS/ritonavir treatment and seek medical evaluation

• New onset or exacerbation of diabetes mellitus and hyperglycemia, and increased bleeding (in patients with hemophilia) have been reported in patients taking protease

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inhibitors. A causal relationship between protease inhibitors and these events has not been established

• A drug interaction study in healthy subjects has shown that ritonavir significantly increases plasma fluticasone propionate exposures. Concomitant use of APTIVUS/ritonavir and fluticasone propionate may produce systemic corticosteroid side effects, including Cushing's syndrome and adrenal suppression. APTIVUS/ritonavir should not be taken with fluticasone propionate, inhaled or intranasally administered, unless the potential benefit to the patient outweighs the risk

• Caution should be used when prescribing sildenafil, tadalafil, or vardenafil with APTIVUS/ritonavir because concentrations of these drugs may increase. Co-administration with rifampin, St. John's wort, lovastatin, or simvastatin is not recommended. This list of medications is not complete

• APTIVUS should be used with caution in patients with a known sulfonamide allergy

• Mild to moderate rashes including urticarial rash, maculopapular rash, and possible photosensitivity have been reported in patients receiving APTIVUS/ritonavir. In some, rash has been accompanied by other symptoms. In one drug interaction trial in healthy female volunteers administered a single dose of ethinyl estradiol followed by APTIVUS/ritonavir, 33% of subjects developed a rash. In Phase 2 and 3 trials, rash was observed in 14% of females and 8% to 10% of males receiving APTIVUS/ritonavir. Women using estrogens may have an increased risk of rash

• Treatment with APTIVUS/ritonavir has resulted in large increases in total cholesterol and triglycerides, which should be monitored prior to and during APTIVUS/ritonavir therapy

• Redistribution and/or accumulation of body fat have been observed in patients receiving antiretroviral therapy. A causal relationship has not been established

• Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including APTIVUS/ritonavir

• In clinical trials, the most frequently reported adverse reactions associated with APTIVUS/ritonavir were diarrhea, nausea, fatigue, vomiting, and headache