Important safety information about Aptivus (tipranavir)

Today (June 30, 2006), Boehringer Ingelheim and FDA informed Healthcare Professionals about important new findings related to Aptivus (tipranavir) capsules, co-administered with ritonavir, 500mg/200mg. Boehringer Ingelheim identified 14 reports of intracranial hemorrhage (ICH) events, including 8 fatalities, in 6,840 HIV-1 infected individuals receiving Aptivus capsules in 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. An increased risk of ICH was previously observed in patients with advanced HIV-1 disease/AIDS. Further investigations are ongoing to assess the role of Aptivus in ICH.

No pattern of abnormal coagulation parameters were observed in patients receiving Aptivus in general, or preceding the development of ICH. Routine measurement of coagulation parameters is not currently indicated in the management of patients on Aptivus. However, in *in vitro* experiments, tipranavir was observed to inhibit human platelet aggregation at levels consistent with exposures observed in patients receiving Aptivus/ritonavir.

According to the *Dear Healthcare Provider* letter, 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.

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)

The new Black Box Warning reads:

"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)"

A pdf copy of the *Dear Healthcare Provider* letter is available in pdf format on the FDA web site at http://www.fda.gov/medwatch/safety/2006/Aptivus-tipranavir_DHCP.pdf

The revised product labeling is available in pdf format at
http://www.fda.gov/medwatch/safety/2006/Aptivus_PI.pdf

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An archive of past list serve announcements is available on the FDA web site at
http://www.fda.gov/oashi/aids/listserve/archive.html