tibotec
THERAPEUTICS
DIVISION OF ORTHO BIOTECH PRODUCTS, L.P.

IMPORTANT DRUG WARNING

March 2008

Dear Healthcare Professional:

Tibotec Therapeutics, in cooperation with the U.S. Food and Drug Administration, would like to inform you of an important update to the prescribing information for PREZISTA™ (darunavir) tablets regarding addition of a Warning on Hepatotoxicity.

In clinical trials and post-marketing experience, drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported in patients receiving combination therapy with PREZISTA/rtv. Given the clinical relevance of this adverse reaction, the following information on hepatotoxicity has been added to the WARNINGS section of the PREZISTA Prescribing Information:

WARNINGS:

Hepatotoxicity

Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported with PREZISTA/rtv. During the clinical development program (N=3063), hepatitis has been reported in 0.5% of patients receiving combination therapy with PREZISTA/rtv. Patients with pre-existing liver dysfunction, including chronic active hepatitis B or C, have an increased risk for liver function abnormalities including severe hepatic adverse events.

Post-marketing cases of liver injury, including some fatalities, have been reported. These have generally occurred in patients with advanced HIV-1 disease taking multiple concomitant medications, having co-morbidities including hepatitis B or C co-infection, and/or developing immune reconstitution syndrome. A causal relationship with PREZISTA/rtv therapy has not been established.

Appropriate laboratory testing should be conducted prior to initiating therapy with PREZISTA/rtv and patients should be monitored during treatment. Increased AST/ALT monitoring should be considered in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases, especially during the first several months of PREZISTA/rtv treatment.

If there is evidence of new or worsening liver dysfunction (including clinically significant elevation of liver enzymes and/or symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, hepatomegaly) in patients on PREZISTA/rtv, interruption or discontinuation of treatment must be considered.

In addition, the Adverse Reaction section of the PREZISTA Prescribing Information and the Patient Package Insert have been updated to include this new information.

Enclosed, please find the updated Prescribing Information as well as the Patient Package Insert.

Please see PREZISTA Indication and additional Important Safety Information included on page 3 and page 4 of this letter.

Tibotec Therapeutics is committed to ensuring that PREZISTA is used safely and effectively and providing you with the most current information for our products.

Should you have any questions, require further information on product safety, or wish to report adverse patient experiences, please contact Tibotec Therapeutics Medical Information at 1-877-REACH TT (1-877-732-2488).

Alternatively, adverse events may be reported to FDA's MedWatch reporting system

- By phone (1-800-FDA-1088), by facsimile (1-800-FDA-0178),
- Online (https://www.accessdata.fda.gov/scripts/medwatch/) or
- Mailed, using the MedWatch for FDA 3500 postage paid form, to the FDA Medical Products Reporting Program, 5600 Fishers Lane, Rockville, MD 20852-9787

Sincerely,

Alan Tennenberg, MD, MPH
Vice President, Clinical Affairs

About PREZISTA

PREZISTA, co-administered with 100 mg ritonavir (PREZISTA/r), and with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV) infection in antiretroviral treatment-experienced adult patients, such as those with HIV-1 strains resistant to more than one protease inhibitor.

This indication is based on Week 24 analyses of plasma HIV RNA levels and CD4+ cell counts from 2 controlled trials of PREZISTA/r in combination with other antiretroviral drugs. Both studies were conducted in clinically advanced, treatment-experienced (NRTIs, NNRTIs, and PIs) adult patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

The following points should be considered when initiating therapy with PREZISTA/r:

- Treatment history and, when available, genotypic or phenotypic testing, should guide the use of PREZISTA/r.

- The use of other active agents with PREZISTA/r is associated with a greater likelihood of treatment response.

- The risks and benefits of PREZISTA/r have not been established in treatment-naïve adult patients or pediatric patients.

Additional Important Safety Information

- Drug Interactions

    - Coadministration of PREZISTA/r is contraindicated with drugs that are highly dependent on CYP3A for clearance and have a narrow therapeutic index (e.g., astemizole, terfenadine, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, pimozide, midazolam, or triazolam) and for which elevated plasma concentrations are associated with serious and/or life-threatening events.
    - Coadministration is not recommended with carbamazepine, phenobarbital, phenytoin, rifampin, lopinavir/ritonavir, saquinavir, lovastatin, pravastatin, simvastatin, or products containing St. John's wort *(Hypericum perforatum)*.
    - Caution should be used when prescribing agents such as sildenafil, vardenafil, tadalafil, or other substrates, inhibitors, or inducers of CYP3A in patients receiving PREZISTA/r**.** This list of potential drug interactions is not complete.

- PREZISTA is contraindicated in patients with known hypersensitivity to any of its ingredients.

- PREZISTA must be co-administered with 100 mg ritonavir and food to exert its therapeutic effect. Failure to correctly administer PREZISTA with ritonavir and food will result in reduced plasma concentration of darunavir that will be insufficient to achieve the desired antiviral effect. Please refer to ritonavir prescribing information for additional information on precautionary measures.

- Severe skin rash, including erythema multiforme and Stevens-Johnson Syndrome has been reported in subjects receiving PREZISTA during the clinical development program. In some cases, fever and elevations of transaminases have also been reported. In clinical trials (n=924), rash (all grades, regardless of causality) occurred in 7% of subjects treated with PREZISTA; discontinuation due to rash was 0.3%. Rashes were generally mild-to-moderate, self-limiting & maculopapular. PREZISTA should be discontinued if severe rash develops.

- PREZISTA should be used with caution in patients with known sulfonamide allergy.

- New-onset or exacerbations of pre-existing diabetes mellitus and hyperglycemia, and increased bleeding in hemophiliacs have been reported in patients receiving protease inhibitors. A causal relationship between protease inhibitors and these events has not been established.

- PREZISTA/r is not recommended for use in patients with severe hepatic impairment. There are no pharmacokinetic or safety data available regarding the use of PREZISTA/r in patients with severe hepatic impairment.

- Redistribution and/or accumulation of body fat have been observed in patients receiving ARV therapy. The casual relationship, mechanism, and long-term consequences of these events have not been established.

- Immune reconstitution syndrome has been reported in patients treated with ARV therapy.

- The potential for HIV-cross-resistance among protease inhibitors has not been fully explored in PREZISTA/r treated patients.

- In the pooled analysis of POWER 1 & 2 studies, the most frequently reported drug-related adverse events of at least moderate to severe intensity in patients receiving PREZISTA/r-containing regimen were headache (3.8%), diarrhea (2.3%), abdominal pain (2.3%), constipation (2.3%), and vomiting (1.5%).

Please see accompanying full Prescribing Information for more details.

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