FDA Approves Prezista®/Ritonavir Once-Daily Dosing for HIV-1 Treatment-Experienced Adults With No Darunavir Resistance-Associated Mutations

[Titusville, NJ, December 13, 2010] - Tibotec Therapeutics, a division of Centocor Ortho Biotech Products, L.P., announced today that the U.S. Food and Drug Administration (FDA) has approved a revision to the dosing recommendation to include once-daily dosing of PREZISTA® (darunavir) tablets in combination with ritonavir for the treatment of human immunodeficiency virus (HIV-1) in treatment-experienced adult patients with no darunavir resistance-associated mutations (DRV RAMs).¹

The revised dosing recommendation extends the same dosing already approved for treatment-naïve patients - PREZISTA, co-administered with ritonavir in combination with other antiretroviral agents and with food, once-daily (800/100 mg) - to treatment-experienced patients with no DRV RAMs. The previously approved dosing recommendation for PREZISTA/ritonavir in treatment-experienced patients (patients who have taken HIV medications in the past) was PREZISTA/ritonavir 600/100 mg twice daily.

For antiretroviral treatment-experienced patients genotypic testing is recommended. However, when genotypic testing is not feasible, PREZISTA/ritonavir 600/100 mg twice daily dosing is recommended.

The approval of this revision is based on 48-week data from the ODIN (Once-daily Darunavir In treatment-experienced patients) study. ODIN evaluated the efficacy and safety of PREZISTA/ritonavir once daily vs. PREZISTA/ritonavir twice daily for the treatment of HIV-1 in treatment-experienced adult patients with no DRV RAMs (i.e., V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, or L89V).³

"With this once-daily dosing recommendation, boosted PREZISTA is now a viable option for more treatment-experienced patients," said Glenn Mattes, president, Tibotec Therapeutics. "This approval reflects Tibotec's ongoing commitment to optimizing dosing strategies for HIV patients."

Data from the Phase 3b ODIN study were presented earlier this year at CROI 2010, the 17th Conference on Retroviruses and Opportunistic Infections, in San Francisco. The study achieved its primary objective of demonstrating non-inferiority of PREZISTA/ritonavir once daily compared with twice daily.

PREZISTA Indication: Adults
PREZISTA, co-administered with ritonavir and with other antiretroviral agents, is indicated for the treatment of HIV-1 infection.

This indication is based on analyses of plasma HIV-1 RNA levels and CD4+ cell counts from two controlled, Phase 3 trials of 48 weeks duration in antiretroviral treatment-naïve and treatment-experienced patients, and two controlled, Phase 2 trials of 96 weeks duration in clinically advanced, treatment-experienced adult patients.

In treatment-experienced adult patients, the following points should be considered when initiating therapy with PREZISTA/ritonavir:

- Treatment history and, when available, genotypic or phenotypic testing, should guide the use of PREZISTA/ritonavir.
- The use of other active agents with PREZISTA/ritonavir is associated with a greater likelihood of treatment response.

About the ODIN Study
ODIN is a Phase 3b, randomized, open-label study that compared the efficacy, safety, and tolerability of PREZISTA/ritonavir 800/100 mg once daily versus PREZISTA/ritonavir 600/100 mg twice daily at week 48 in 590 treatment-experienced HIV-1-infected adult patients with no DRV RAMs (V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, or L89V). Patients had HIV-1 RNA greater than 1,000 copies/mL and CD4 count greater than 50 cells/mm³, and received a stable antiretroviral therapy regimen for greater than or equal to 12 weeks at screening. Patients received either once-daily (n=294) or twice-daily (n=296) PREZISTA/ritonavir plus optimized background regimen. The primary objective of the study was to demonstrate non-inferiority of PREZISTA/ritonavir 800/100 mg once-daily versus PREZISTA/ritonavir 600/100 mg twice-daily in confirmed virologic response (HIV-1 RNA less than 50 copies/mL [intent-to-treat/time-to-loss of virologic response; ITT-TLOVR]) at Week 48.

Important Safety Information
PREZISTA does not cure HIV-1 infection or AIDS, and does not prevent passing HIV-1 to others.

Drug Interactions
Coadministration of PREZISTA/ritonavir is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events (e.g., alfuzosin, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, pimozide, oral midazolam, triazolam, lovastatin, or simvastatin).

Coadministration of PREZISTA/ritonavir is also contraindicated with rifampin and products containing St. John's wort (Hypericum perforatum) because this may cause significant decrease in plasma concentration of darunavir, resulting in loss of therapeutic effect and development of resistance.

Coadministration is not recommended with indinavir, lopinavir/ritonavir, saquinavir, and pravastatin.

Caution should be used when prescribing agents such as sildenafil, vardenafil, tadalafil, or other substrates, inhibitors, or inducers of CYP3A in patients receiving PREZISTA/ritonavir.

This list of potential drug interactions is not complete.

Warnings & Precautions

PREZISTA must be coadministered with ritonavir and food to achieve the desired antiviral effect. Failure to administer PREZISTA with ritonavir and food may result in a loss of efficacy of darunavir. Please refer to ritonavir prescribing information for additional information on precautionary measures.

Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported with PREZISTA/ritonavir. During the clinical development program (N=3063), hepatitis has been reported in 0.5% of patients receiving combination therapy with PREZISTA/ritonavir. Patients with preexisting 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. A causal relationship with PREZISTA/ritonavir therapy has not been established.

Appropriate laboratory testing should be conducted prior to initiating therapy with PREZISTA/ritonavir 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 pretreatment elevations of transaminases, especially during the first several months of PREZISTA/ritonavir treatment. Evidence of new or worsening liver dysfunction (including clinically significant elevation of liver enzymes and/or symptoms such as fatigue, anorexia, jaundice, dark urine, liver tenderness, hepatomegaly) in patients on PREZISTA/ritonavir should prompt consideration of interruption or discontinuation of treatment.

Severe Skin Reactions: Severe skin reactions (0.4%), accompanied by fever and/or elevations of transaminases in some cases, Stevens-Johnson Syndrome (<0.1%), and toxic epidermal necrolysis (post-marketing experience) have been reported in patients receiving PREZISTA/ritonavir. Discontinue PREZISTA/ritonavir immediately if signs or symptoms of severe skin reactions develop (including, but not limited to, severe rash or rash accompanied with fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis and/or eosinophilia).

In clinical trials (N=3063), rash (all grades, generally mild to moderate, regardless of causality) occurred in 10.3% of patients receiving PREZISTA/ritonavir. Discontinuation due to rash was 0.5%.

Sulfa Allergy: PREZISTA should be used with caution in patients with known sulfonamide allergy.

Diabetes Mellitus/Hyperglycemia and Hemophilia: New-onset or exacerbations of preexisting diabetes mellitus, hyperglycemia, and increased bleeding in hemophiliacs have been reported in patients receiving protease inhibitors. Initiation or dose adjustments of insulin or oral hypoglycemic agents may be required. A causal relationship between protease inhibitors and these events has not been established.

Fat Redistribution: Redistribution and/or accumulation of body fat have been observed in patients receiving ARV therapy. The causal 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.

Resistance/Cross Resistance: The potential for HIV-1 cross-resistance among protease inhibitors has not been fully explored in PREZISTA/ritonavir-treated patients.

Use in Specific Populations

Hepatic Impairment: PREZISTA/ritonavir is not recommended for use in patients with severe hepatic impairment. There are no pharmacokinetic or safety data available in patients with severe hepatic impairment.

Pregnancy: PREZISTA should be used during pregnancy only if the potential benefit justifies the potential risk. No adequate and well-controlled studies have been conducted in pregnant women.

Adverse Reactions

In treatment-naïve adult patients, the most common adverse drug reactions (5%) reported of at least moderate intensity (≥Grade 2) in the PREZISTA/ritonavir arm through 96 weeks were diarrhea (8%), headache (6%), abdominal pain (5%), and rash (5%).

In treatment-experienced adult patients, the most common adverse drug reactions (5%) reported of at least...
moderate intensity (≥ Grade 2) in the PREZISTA/ritonavir arm through 96 weeks were diarrhea (14%), nausea (7%), rash (7%), abdominal pain (6%), and vomiting (5%)

This is not a complete list of all adverse drug reactions reported with the use of PREZISTA/ritonavir.

Please see accompanying full Prescribing Information for more details. Full prescribing information is also available at www.PREZISTA.com.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

About Tibotec Pharmaceuticals
Tibotec Pharmaceuticals, based in Cork, Ireland, is a pharmaceutical research and development company. The Company's main research and development facilities are in Beerse, Belgium, with offices in Titusville, NJ, USA. Tibotec is dedicated to the discovery and development of innovative HIV-1/AIDS drugs and anti-infectives for diseases of high unmet medical need.

About Tibotec Therapeutics
Tibotec Therapeutics, a division of Centocor Ortho Biotech Products, L.P., headquartered in Titusville, NJ, is dedicated to delivering innovative virology therapeutics that help healthcare professionals address serious unmet needs in people living with HIV-1.

1 Resistance-associated mutations are also referred to as resistance-associated substitutions.