

New Drug Bulletin: Darunavir (Prezista™ - Tibotec, Inc.)

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Darunavir (Prezista™) is a protease inhibitor (PI) labeled for the treatment of human immunodeficiency disorder (HIV) in antiretroviral treatment-experienced patients. Treatment-experienced patients include those with HIV-1 strains resistant to at least one PI. There are currently no data in treatment-naïve or pediatric HIV patients. HIV-1 strains resistant to other PIs are likely susceptible to darunavir. Once resistance develops to darunavir, cross-resistance to other PIs is likely, excluding tipranavir. Use darunavir in combination with ritonavir and other antiretroviral therapies.

Darunavir has a low bioavailability when taken alone. It is a substrate and inhibitor of CYP 3A and must be administered with ritonavir, a CYP 3A inhibitor, to achieve adequate bioavailability. It also must be taken with food, which increases the bioavailability by ~30%. Darunavir is 95% protein-bound. It is metabolized extensively by CYP 3A. Darunavir is excreted in the feces (41.2% unchanged) and urine (7.7% unchanged). When administered with ritonavir, darunavir's terminal half life is approximately 15 hours. Dosage adjustments may be required in patients with hepatic impairment although there are no data in this population. No dosage adjustments are required based on Hepatitis B Virus or Hepatitis C Virus coinfection, renal impairment (including hemodialysis and peritoneal dialysis), age, gender, or race.

Safety and efficacy data were obtained in two similar 24-week randomized controlled trials in a total of 637 patients. Patients in the treatment group received darunavir/ritonavir 600/100 mg combined with an optimized background regimen (OBR) consisting of at least two nucleotide reverse transcriptase inhibitors (NRTIs) with or without enfuvirtide. The comparator group received an investigator-chosen PI based on disease genotype and phenotype combined with an OBR. Patients included in the study had plasma HIV-1 RNA greater than 1000 copies/mL; prior treatment with a PI, non-nucleotide reverse transcriptase inhibitor (NNRTI), or NRTI; a stable PI regimen during the 8 weeks prior to the study; and at least one PI mutation. Response to therapy was defined as a 1 log₁₀ decrease in HIV-1 RNA viral load from baseline at week 24. The response rate was 69.5% for the darunavir group versus 21% for the comparator group.

More than 10% of patients that received darunavir experienced diarrhea, nausea, headache, or nasopharyngitis. Skin rash, fat redistribution, and Immune Reconstitution Syndrome are also possible side effects of darunavir. Use darunavir with caution in patients with hepatic impairment, sulfonamide allergies, diabetes mellitus, or hemophilia. Drugs that inhibit or induce CYP 3A can greatly alter the effects of darunavir. Narrow therapeutic index drugs metabolized by CYP 3A are contraindicated with darunavir. Carefully assess the use of drugs affected by CYP 3A when considering darunavir therapy.

Darunavir is available as a 300 mg tablet. The recommended dose is 600 mg twice daily (BID) in combination with ritonavir 100 mg BID. Before using darunavir, it is important to obtain a thorough HIV treatment history as well as disease genotype or phenotype if available to assess appropriateness of therapy.

Table 1 provides a cost comparison of darunavir with a second therapeutic option for treatment-experienced HIV patients (tipranavir [Aptivus®]). Average Wholesale Price (AWP) and Wholesale Acquisition Cost (WAC) for a 30-day supply of each regimen are provided.

Table 1. Cost Comparison of Darunavir (Prezista™) and Tipranavir (Aptivus®)

Drug	Formulation	Regimen	AWP (30 day supply)	WAC (30 day supply)
Darunavir	300 mg tablet	600 mg b.i.d.	\$937.50	\$750.00
Ritonavir	100 mg capsule	100 mg b.i.d.	<u>\$642.95</u>	<u>\$514.36</u>
			\$1,580.45 total	\$1,264.36 total
Tipranavir	250 mg capsule	500 mg b.i.d.	\$1117.50	\$894.00
Ritonavir	100 mg capsule	200 mg b.i.d.	<u>\$1285.89</u>	<u>\$1028.71</u>
			\$2,403.39 total	\$2,022.71 total

In summary, darunavir is a viable treatment option for treatment-experienced HIV patients when used in combination with ritonavir and other antiretroviral therapies. Educate patients that administration with ritonavir and food is imperative for adequate bioavailability of this drug. Monitor for potential drug interactions to minimize treatment failures and adverse events.

References:

1. Prezista™ (darunavir) package insert. Raritan, NJ: Ortho Biotech Products; June 2006.
2. Aptivus® (tipranavir) package insert. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; June 2006.

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