CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-976

APPROVED LABELING

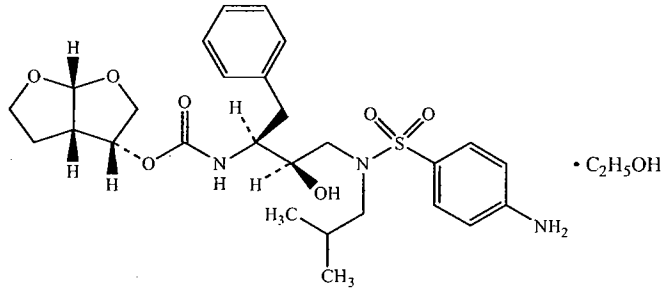
PREZISTA™* (Tibotec, Inc.)
(darunavir)

Tablets

DESCRIPTION

PREZISTA™ (darunavir) is an inhibitor of the human immunodeficiency virus (HIV) protease.

PREZISTA™ (darunavir), in the form of darunavir ethanolate, has the following chemical name: [(1*S*,2*R*)-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-yl ester monoethanolate. Its molecular formula is $C_{27}H_{37}N_3O_7S \cdot C_2H_5OH$ and its molecular weight is 593.73. Darunavir ethanolate has the following structural formula:



Darunavir ethanolate is a white to off-white powder with a solubility of approximately 0.15 mg/mL in water at 20°C.

PREZISTA is available as an orange, oval-shaped, film-coated tablet for oral administration. Each tablet contains darunavir ethanolate equivalent to 300 mg of darunavir. Each tablet also contains the inactive ingredients colloidal silicon dioxide, crospovidone, magnesium stearate, and microcrystalline cellulose. The tablet film coating, OPADRY® Orange, contains FD&C Yellow No. 6, polyethylene glycol 3350, polyvinyl alcohol-partially hydrolyzed, talc, and titanium dioxide.

All dosages for PREZISTA are expressed in terms of the free form of darunavir.

MICROBIOLOGY

Mechanism of Action

Darunavir is an inhibitor of the HIV-1 protease. It selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in infected cells, thereby preventing the formation of mature virus particles.

Antiviral Activity

Darunavir exhibits activity against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV-2 in acutely infected T-cell lines, human peripheral blood mononuclear cells and human monocytes/macrophages with median EC_{50} values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/mL). Darunavir demonstrates antiviral activity in cell culture against a broad panel of HIV-1 group M (A, B, C, D, E, F, G), and group O primary isolates with EC_{50} values ranging from < 0.1 to 4.3 nM. The EC_{50} value of darunavir increases by a median factor of 5.4 in the presence of human serum. Darunavir did not show antagonism when studied in combination with the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, or tipranavir, the N(t)RTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, or zidovudine, the NNRTIs delavirdine, efavirenz, or nevirapine, and the fusion inhibitor enfuvirtide.

Resistance

Cell Culture: HIV-1 isolates with a decreased susceptibility to darunavir have been selected in cell culture and obtained from subjects treated with darunavir/ritonavir. Darunavir-resistant virus derived in cell culture from wild-type HIV had 6- to 21-fold decreased susceptibility to darunavir and harbored 3 to 6 of the following amino acid substitutions S37N/D, R41E/S/T, K55Q, K70E, A71T, T74S, V77I, or I85V in the protease. Selection in cell culture of darunavir resistant HIV-1 from nine HIV-1 strains harboring multiple protease inhibitor resistance-associated mutations resulted in the overall emergence of 22 mutations in the protease gene, including L10F, V11I, I13V, I15V, G16E, L23I, V32I, L33F, S37N, M46I, I47V, I50V, F53L, L63P, A71V, G73S, L76V, V82I, I84V, T91A/S, and Q92R, of which L10F, V32I, L33F, S37N, M46I, I47V, I50V, L63P, A71V, and I84V were the most prevalent. These darunavir-resistant viruses had at least eight protease mutations and exhibited 50- to 641-fold decreases in darunavir susceptibility with final EC_{50} values ranging from 125 nM to 3461 nM.

Clinical studies of darunavir/ritonavir in treatment-experienced subjects

In the Phase 2b Studies TMC114-C213 and TMC114-C202 and the TMC114-C215/C208 analysis, multiple protease inhibitor-resistant HIV-1 isolates from highly treatment-experienced subjects who received PREZISTA/rtv 600/100 mg b.i.d. and experienced virologic failure, either by rebound, or by never being suppressed, developed amino acid substitutions that were associated with a decrease in susceptibility to darunavir. The amino acid substitution V32I developed on PREZISTA/rtv 600/100 mg b.i.d. in greater than 30% of virologic failure isolates and substitutions at amino acid position I54 developed in greater than 20% of virologic failure isolates. Other substitutions that developed in 10% to 20% of PREZISTA/rtv virologic failure isolates occurred at amino acid positions I15, L33, I47, G73 and L89. The median darunavir phenotype (fold change from reference) of the virologic failure isolates was 21-fold at baseline and 94-fold at failure. Amino acid substitutions were also observed in the protease cleavage sites of some darunavir virologic failure isolates. The resistance profile in treatment-naïve subjects has not been characterized.

Cross-resistance

Cross-resistance among protease inhibitors has been observed. Darunavir has a < 10-fold decreased susceptibility in cell culture against 90% of 3309 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and/or tipranavir showing that viruses resistant to these protease inhibitors remain susceptible to darunavir. In Studies TMC114-C213 and TMC114-C202 and the TMC114-C215/C208 analysis, 60% (88/147) of subjects on darunavir/rtv whose baseline isolates had decreased susceptibility to tipranavir (tipranavir fold change > 3) demonstrated a decrease of ≥ 1 $\log_{10}$ in viral load at week 24, and 36% (53/147) achieved < 50 copies/mL plasma HIV RNA levels.

Darunavir-resistant viruses were not susceptible to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir or saquinavir in cell culture. However, six of nine darunavir-resistant viruses selected in cell culture from protease inhibitor-resistant viruses showed a fold change in EC_{50} values < 3 for tipranavir, indicative of limited cross-resistance between darunavir and tipranavir. Of the viruses isolated from subjects experiencing virologic failure on darunavir/ritonavir 600/100 mg b.i.d., greater than 50% were still susceptible to tipranavir while less than 5% were susceptible to other protease inhibitors (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, or saquinavir).

Cross-resistance between darunavir and the nucleoside/nucleotide reverse transcriptase inhibitors, the non-nucleoside reverse transcriptase inhibitors or the fusion inhibitor is unlikely because the viral targets are different.

Baseline Genotype/Phenotype and Virologic Outcome Analyses

Genotypic and/or phenotypic analysis of baseline virus may aid in determining darunavir susceptibility before initiation of PREZISTA/rtv 600/100 mg b.i.d. therapy. Analyses were conducted to evaluate the impact of specific baseline protease inhibitor resistance-associated mutations and the number of protease inhibitor resistance-associated mutations at baseline on virologic response. Both specific mutations and the number of baseline mutations, as well as susceptible drugs in the optimized background regimen and enfuvirtide use, affected PREZISTA/rtv response rates in Phase 2b Studies TMC114-C213 and TMC114-C202.

The presence at baseline of the mutations V32I, I47V, or I54L or M, was associated with a decreased virologic response to darunavir and decreased susceptibility to darunavir. In addition, a diminished virologic response was observed in subjects with ≥ 7 protease inhibitor resistance-associated mutations (any change at amino acid positions 30, 32, 36, 46, 47, 48, 50, 53, 54, 73, 82, 84, 88, or 90) at baseline (see Table 1). In a supportive analysis of Studies TMC114-C213 and TMC114-C202 and the TMC114-C215/C208 analysis, the presence at baseline of three or more of the mutations V11I, V32I, L33F, I47V, I50V, I54L or M, G73S, L76V, I84V or L89V was associated with a decreased virologic response to PREZISTA/rtv (the proportion of subjects achieving viral load < 50 plasma HIV RNA copies/mL at week 24 was 50%, 22% and 10% when the baseline genotype had 0-2, 3 and ≥ 4 of these mutations, respectively). Conclusions regarding

the relevance of particular mutations or mutational patterns are subject to change pending additional data.

Table 1: Response to PREZISTA/rtv 600/100 mg b.i.d. by Baseline Number of Protease Inhibitor Resistance-Associated Mutations: As-Treated Analysis of Studies TMC114-C213 and TMC114-C202

	Prezista/rtv 600/100 mg (n = 125)				Comparative Arm (n = 120)			
PI Mutations^	**n**	**Proportion of subjects with ≥ 1 log_{10} decrease at Week 24**	**Proportion of subjects with < 50 copies /mL at Week 24**	**Median $DAVG_{24}$**	**n**	**Proportion of subjects with ≥ 1 log_{10} decrease at Week 24**	**Proportion of subjects with < 50 copies /mL at Week 24**	**Median $DAVG_{24}$**
0 - 4	57	81%	46%	-2.16	52	23%	13%	-0.57
5 - 6	54	67%	52%	-2.13	51	24%	16%	-0.43
≥ 7	14	21%	14%	-0.87	17	6%	0%	-0.13

^ Any change at protease amino acid positions 30, 32, 36, 46, 47, 48, 50, 53, 54, 73, 82, 84, 88 and 90

Baseline darunavir phenotype (shift in susceptibility relative to reference) was shown to be a predictive factor of virologic outcome. Response rates assessed by baseline darunavir phenotype are shown in Table 2. These baseline phenotype groups are based on the select subject populations in the Studies TMC114-C213 and TMC114-C202 and the TMC114-C215/C208 analysis, and are not meant to represent definitive clinical susceptibility breakpoints for PREZISTA/rtv. The data are provided to give clinicians information on the likelihood of virologic success based on pre-treatment susceptibility to darunavir in protease inhibitor-experienced patients.

Table 2: Response to PREZISTA/rtv 600/100 mg b.i.d. by Baseline Darunavir Phenotype: As-Treated Analysis of Studies TMC114-C213, TMC114-C202, and TMC114-C215/C208

Baseline Darunavir Phenotype N = 340 (fold change ranges)	**Proportion of subjects with ≥1 log_{10} decrease at Week 24**	**Proportion of subjects with < 50 copies/mL at Week 24**	**Clinical Response Range**
All ranges	70% 238/340	43% 147/340	Overall Response
0 - 2	88% 119/136	60% 82/136	Higher than Overall Response
> 2 - 7	73% 62/85	47% 40/85	Similar to Overall Response
> 7 - 30	52% 33/63	24% 15/63	Lower than Overall Response
> 30	43% 24/56	18% 10/56	Lower than Overall Response

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