Table 10: Drug Interactions: Pharmacokinetic Parameters for Darunavir in the Presence of Co-administered Drugs

Co-Administered Drug	Dose/Schedule		N	PK	LS Mean Ratio (90% CI) of Darunavir Pharmacokinetic Parameters With/Without Co-administered Drug No Effect =1.00		
	Co-Administered Drug	Darunavir/ ritonavir			C_{max}	AUC	C_{min}
Co-Administration With Other Protease Inhibitors							
Atazanavir	300 mg q.d.*	400/100 mg b.i.d. †	13	↔	1.02 (0.96-1.09)	1.03 (0.94-1.12)	1.01 (0.88-1.16)
Indinavir	800 mg b.i.d.	400/100 mg b.i.d.	9	↑	1.11 (0.98-1.26)	1.24 (1.09-1.42)	1.44 (1.13-1.82)
Lopinavir/ Ritonavir	400/100 mg b.i.d.	1200/100 mg b.i.d.‡	14	↓	0.79 (0.67-0.92)	0.62 (0.53-0.73)	0.49 (0.39-0.63)
	533/133.3 mg b.i.d.	1200 mg b.i.d.‡	15	↓	0.79 (0.64-0.97)	0.59 (0.50-0.70)	0.45 (0.38-0.52)
Saquinavir hard gel capsule	1000 mg b.i.d.	400/100 mg b.i.d.	14	↓	0.83 (0.75-0.92)	0.74 (0.63-0.86)	0.58 (0.47-0.72)
Co-Administration With Other Antiretrovirals							
Didanosine	400 mg q.d.	600/100 mg b.i.d.	17	↔	0.93 (0.86-1.00)	1.01 (0.95-1.07)	1.07 (0.95-1.21)
Efavirenz	600 mg q.d.	300/100 mg b.i.d.	12	↓	0.85 (0.72-1.00)	0.87 (0.75-1.01)	0.69 (0.54-0.87)
Etravirine	200 mg b.i.d.	600/100 mg b.i.d.	15	↔	1.11 (1.01-1.22)	1.15 (1.05-1.26)	1.02 (0.90-1.17)
Nevirapine	200 mg b.i.d.	400/100 mg b.i.d.	8	↑	1.40 § (1.14-1.73)	1.24 § (0.97-1.57)	1.02 § (0.79-1.32)
Tenofovir Disoproxil Fumarate	300 mg q.d.	300/100 mg b.i.d.	12	↑	1.16 (0.94-1.42)	1.21 (0.95-1.54)	1.24 (0.90-1.69)
Co-Administration With Other Drugs							
Carbamazepine	200 mg b.i.d.	600/100 mg b.i.d.	16	↔	1.04 (0.93-1.16)	0.99 (0.90-1.08)	0.85 (0.73-1.00)
Clarithromycin	500 mg b.i.d.	400/100 mg b.i.d.	17	↔	0.83 (0.72-0.96)	0.87 (0.75-1.01)	1.01 (0.81-1.26)
Ketoconazole	200 mg b.i.d.	400/100 mg b.i.d.	14	↑	1.21 (1.04-1.40)	1.42 (1.23-1.65)	1.73 (1.39-2.14)
Omeprazole	20 mg q.d.	400/100 mg b.i.d.	16	↔	1.02 (0.95-1.09)	1.04 (0.96-1.13)	1.08 (0.93-1.25)
Paroxetine	20 mg q.d.	400/100 mg b.i.d.	16	↔	0.97 (0.92-1.02)	1.02 (0.95-1.10)	1.07 (0.96-1.19)
Ranitidine	150 mg b.i.d.	400/100 mg b.i.d.	16	↔	0.96 (0.89-1.05)	0.95 (0.90-1.01)	0.94 (0.90-0.99)
Rifabutin	150 mg q.o.d. ¶	600/100 mg b.i.d.	11	↑	1.42 (1.21-1.67)	1.57 (1.28-1.93)	1.75 (1.28-2.37)
Sertraline	50 mg q.d.	400/100 mg b.i.d.	13	↔	1.01 (0.89-1.14)	0.98 (0.84-1.14)	0.94 (0.76-1.16)

N = number of subjects with data; - = no information available.

[*] q.d. = once daily
[†] b.i.d. = twice daily
[‡] The pharmacokinetic parameters of darunavir in this study were compared with the pharmacokinetic parameters following administration of darunavir/ritonavir 600/100 mg b.i.d.
[§] Ratio based on between-study comparison.
[¶] q.o.d. = every other day

Table 11:	**Drug Interactions: Pharmacokinetic Parameters for Co-administered Drugs in the Presence of Darunavir/Ritonavir**						
	Dose/Schedule				**LS Mean Ratio (90% CI) of Co-Administered Drug Pharmacokinetic Parameters With/Without Darunavir No effect =1.00**		
Co-Administered Drug	**Co-Administered Drug**	**Darunavir/ ritonavir**	**N**	**PK**	**C_{max}**	**AUC**	**C_{min}**
Co-Administration With Other Protease Inhibitors							
Atazanavir	300 mg q.d.* /100 mg ritonavir q.d. when administered alone 300 mg q.d. when administered with darunavir/ ritonavir	400/100 mg b.i.d. †	13	↔	0.89 (0.78-1.01)	1.08 (0.94-1.24)	1.52 (0.99-2.34)
Indinavir	800 mg b.i.d. /100 mg ritonavir b.i.d. when administered alone 800 mg b.i.d. when administered with darunavir/ ritonavir	400/100 mg b.i.d.	9	↑	1.08 (0.95-1.22)	1.23 (1.06-1.42)	2.25 (1.63-3.10)
Lopinavir/ Ritonavir	400/100 mg b.i.d.‡	1200/100 mg b.i.d.	14	↔	0.98 (0.78-1.22)	1.09 (0.86-1.37)	1.23 (0.90-1.69)
	533/133.3 mg b.i.d.‡	1200 mg b.i.d.	15	↔	1.11 (0.96-1.30)	1.09 (0.96-1.24)	1.13 (0.90-1.42)
Saquinavir hard gel capsule	1000 mg b.i.d. /100 mg ritonavir b.i.d. when administered alone 1000 mg b.i.d. when administered with darunavir/ ritonavir	400/100 mg b.i.d.	12	↔	0.94 (0.78-1.13)	0.94 (0.76-1.17)	0.82 (0.52-1.30)
Co-Administration With Other Antiretrovirals							
Didanosine	400 mg q.d.	600/100 mg b.i.d.	17	↔	0.84 (0.59-1.20)	0.91 (0.75-1.10)	-
Efavirenz	600 mg q.d.	300/100 mg b.i.d.	12	↑	1.15 (0.97-1.35)	1.21 (1.08-1.36)	1.17 (1.01-1.36)
Etravirine	100 mg b.i.d.	600/100 mg b.i.d.	14	↓	0.68	0.63	0.51

					(0.57-0.82)	(0.54-0.73)	(0.44-0.61)
Nevirapine	200 mg b.i.d.	400/100 mg b.i.d.	8	↑	1.18 (1.02-1.37)	1.27 (1.12-1.44)	1.47 (1.20-1.82)
Tenofovir Disoproxil Fumarate	300 mg q.d.	300/100 mg b.i.d.	12	↑	1.24 (1.08-1.42)	1.22 (1.10-1.35)	1.37 (1.19-1.57)
Maraviroc	150 mg b.i.d.	600/100 mg b.i.d.	12	↑	2.29 (1.46-3.59)	4.05 (2.94-5.59)	8.00 (6.35-10.1)
Maraviroc	150 mg b.i.d.	600/100 mg b.i.d. with 200 mg b.i.d. etravirine	10	↑	1.77 (1.20-2.60)	3.10 (2.57-3.74)	5.27 (4.51-6.15)
Co-Administration With Other Drugs							
Atorvastatin	40 mg q.d. when administered alone 10 mg q.d. when administered with darunavir/ ritonavir	300/100 mg b.i.d.	15	↑	0.56 (0.48-0.67)	0.85 (0.76-0.97)	1.81 (1.37-2.40)
Buprenorphine/ Naloxone	8/2 mg to 16/4 mg q.d.	600/100 mg b.i.d.	17	↔	0.92 [§] (0.79-1.08)	0.89 [§] (0.78-1.02)	0.98 [§] (0.82-1.16)
Norbuprenorphine			17	↑	1.36 (1.06-1.74)	1.46 (1.15-1.85)	1.71 (1.29-2.27)
Carbamazepine	200 mg b.i.d.	600/100 mg b.i.d.	16	↑	1.43 (1.34-1.53)	1.45 (1.35-1.57)	1.54 (1.41-1.68)
Carbamazepine epoxide			16	↓	0.46 (0.43-0.49)	0.46 (0.44-0.49)	0.48 (0.45-0.51)
Clarithromycin	500 mg b.i.d.	400/100 mg b.i.d.	17	↑	1.26 (1.03-1.54)	1.57 (1.35-1.84)	2.74 (2.30-3.26)
Dextromethorphan	30 mg	600/100 mg b.i.d.	12	↑	1.27 (1.58-3.25)	1.70 (1.80-4.05)	-
Dextrorphan				↓	0.86 (0.76-0.97)	0.96 (0.89-1.03)	-
Digoxin	0.4 mg	600/100 mg b.i.d.	8	↑	1.15 (0.89-1.48)	1.36 (0.81-2.27)	-

Ethinyl Estradiol (EE)	Ortho-Novum 1/35 (35 µg EE / 1 mg NE)	600/100 mg b.i.d.	11	↓	0.68 (0.61-0.74)	0.56 (0.50-0.63)	0.38 (0.27-0.54)
Norethindrone (NE)			11	↓	0.90 (0.83-0.97)	0.86 (0.75-0.98)	0.70 (0.51-0.97)
Ketoconazole	200 mg b.i.d.	400/100 mg b.i.d.	15	↑	2.11 (1.81-2.44)	3.12 (2.65-3.68)	9.68 (6.44-14.55)
R-Methadone	55-150 mg q.d.	600/100 mg b.i.d.	16	↓	0.76 (0.71-0.81)	0.84 (0.78-0.91)	0.85 (0.77-0.94)
Omeprazole	40 mg single dose	600/100 mg b.i.d.	12	↓	0.66 (0.48-0.90)	0.58 (0.50-0.66)	-
5-hydroxy omeprazole				↓	0.93 (0.71-1.21)	0.84 (0.77-0.92)	-
Paroxetine	20 mg q.d.	400/100 mg b.i.d.	16	↓	0.64 (0.59-0.71)	0.61 (0.56-0.66)	0.63 (0.55-0.73)
Pravastatin	40 mg single dose	600/100 mg b.i.d.	14	↑	1.63 (0.95-2.82)	1.81 (1.23-2.66)	-
Rifabutin	150 mg q.o.d. ¶ when administered with PREZISTA/ritonavir 300 mg q.d. when administered alone	600/100 mg b.i.d. #	11	↑	0.72 (0.55-0.93)	0.93 (0.80-1.09)	1.64 (1.48-1.81)
25-*O*-desacetyl-rifabutin			11	↑	4.77 (4.04-5.63)	9.81 (8.09-11.9)	27.1 (22.2-33.2)
Sertraline	50 mg q.d.	400/100 mg b.i.d.	13	↓	0.56 (0.49-0.63)	0.51 (0.46-0.58)	0.51 (0.45-0.57)
Sildenafil	100 mg (single dose) administered alone 25 mg (single dose) when administered with darunavir/ ritonavir	400/100 mg b.i.d.	16	↑	0.62 (0.55-0.70)	0.97 (0.86-1.09)	-
S-warfarin	10 mg single dose	600/100 mg b.i.d.	12	↓	0.92 (0.86-0.97)	0.79 (0.73-0.85)	-
7-OH-S-warfarin			12	↑	1.42 (1.24-1.63)	1.23 (0.97-1.57)	-
N = number of subjects with data;- = no information available.							

[*] q.d. = once daily
[†] b.i.d. = twice daily
[‡] The pharmacokinetic parameters of lopinavir in this study were compared with the pharmacokinetic parameters following administration of lopinavir/ritonavir 400/100 mg b.i.d.
[§] ratio is for buprenorphine; mean C_{max} and AUC_{24} for naloxone were comparable when buprenorphine/naloxone was administered with or without PREZISTA/ritonavir
[¶] q.o.d. = every other day
[#] In comparison to rifabutin 300 mg q.d.
A cocktail study was conducted in 12 healthy volunteers to evaluate the effect of steady state pharmacokinetics of darunavir/ritonavir on the activity of CYP2D6 (using dextromethorphan as probe substrate), CYP2C9 (using warfarin as probe substrate), and CYP2C19 (using omeprazole as probe substrate). The pharmacokinetic results are shown in Table 11.

12.4 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 PIs 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, etravirine, 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 21- to 88-fold decreased susceptibility to darunavir and developed 2 to 4 of the following amino acid substitutions S37D, R41E/T, K55Q, H69Q, K70E, T74S, V77I, or I85V in the protease. Selection in cell culture of darunavir resistant HIV-1 from nine HIV-1 strains harboring multiple PI resistance-associated mutations resulted in the overall emergence of 22 mutations in the protease gene, coding for amino acid substitutions 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 substitutions 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 PREZISTA/ritonavir in treatment-experienced subjects: In a pooled analysis of the 600/100 mg PREZISTA/ritonavir twice daily arms of Studies TMC114-C213, TMC114-C202, TMC114-C215, and the control arms of etravirine studies TMC125-C206 and TMC125-C216, the amino acid substitutions V32I and I54L or M developed most frequently on PREZISTA/ritonavir in 41% and 25%, respectively, of the treatment-experienced subjects who experienced virologic failure, either by rebound or by never being suppressed (< 50 copies/mL). Other substitutions that developed frequently in PREZISTA/ritonavir virologic failure isolates occurred at amino acid positions V11I, I15V, L33F, I47V, I50V, and L89V. These amino acid substitutions were associated with decreased susceptibility to darunavir; 90% of the virologic failure isolates had a > 7-fold decrease in susceptibility to darunavir at failure. The median darunavir phenotype (fold change from reference) of the virologic failure isolates was 4.3-fold at baseline and 85-fold at failure. Amino acid substitutions were also observed in the protease cleavage sites in the Gag polyprotein of some PREZISTA/ritonavir virologic failure isolates. In Study TMC114-C212 of treatment-experienced pediatric subjects, the amino acid substitutions V32I, I54L and L89M developed most frequently in virologic failures on PREZISTA/ritonavir.

In the 96-week as-treated analysis of the Phase 3 Study TMC114-C214, the percent of virologic failures (never suppressed, rebounders and discontinued before achieving suppression) was 21% (62/298) in the group of subjects receiving PREZISTA/ritonavir 600/100 mg twice daily compared to 32% (96/297) of subjects receiving lopinavir/ritonavir 400/100 mg twice daily. Examination of subjects who failed on PREZISTA/ritonavir 600/100 mg twice daily and had post-baseline genotypes and phenotypes showed that 7 subjects (7/43; 16%) developed PI substitutions on darunavir/ritonavir treatment resulting in decreased susceptibility to darunavir. Six of the 7 had baseline PI resistance-associated substitutions and baseline darunavir phenotypes > 7. The most common emerging PI substitutions in these virologic failures were V32I, L33F, M46I or L, I47V, I54L, T74P and L76V. These amino acid substitutions were associated with 59- to 839-fold decreased susceptibility to darunavir at failure. Examination of individual subjects who failed in the comparator arm on lopinavir/ritonavir and had post-baseline genotypes and phenotypes showed that 31 subjects (31/75; 41%) developed substitutions on lopinavir treatment resulting in decreased susceptibility to lopinavir (> 10-fold) and the most common substitutions emerging on treatment were L10I or F, M46I or L, I47V or A, I54V and L76V. Of the 31 lopinavir/ritonavir virologic failure subjects, 14 had reduced susceptibility (> 10-fold) to lopinavir at baseline.

Clinical studies of PREZISTA/ritonavir in treatment-naive subjects: In the 96-week as-treated analysis of the Phase 3 Study TMC114-C211, the percentage of virologic failures (never suppressed, rebounders and discontinued before achieving suppression) was 15% (53/343) in the group of subjects receiving PREZISTA/ritonavir 800/100 mg once daily compared to 22% (77/346) of subjects receiving lopinavir/ritonavir 800/200 mg per day. In the PREZISTA/ritonavir arm, emergent PI substitutions were identified in 5 of the virologic failures with post-baseline genotypic data (n=14). However, none of the darunavir virologic failures had a decrease in darunavir susceptibility (> 7-fold change) at failure. In the comparator lopinavir/ritonavir arm, emergent PI substitutions were identified in 15 of the virologic failures with post-baseline genotypic data (n=28), but none of the lopinavir/ritonavir virologic failures had decreased susceptibility to lopinavir (> 10-fold change) at failure. The reverse transcriptase M184V substitution and resistance to emtricitabine, which was included in the fixed background regimen, was identified in 2 virologic failures of the PREZISTA/ritonavir arm and 3 virologic failures in the lopinavir/ritonavir arm.

Cross-resistance

Cross-resistance among PIs 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 PIs remain susceptible to darunavir.

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 PI-resistant viruses showed a fold change in EC_{50} values < 3 for tipranavir, indicative of limited cross-resistance between darunavir and tipranavir. In Studies TMC114-C213, TMC114-C202, and TMC114-C215, 34% (64/187) of subjects in the darunavir/ritonavir arm whose baseline isolates had decreased susceptibility to tipranavir (tipranavir fold change > 3) achieved < 50 copies/mL serum HIV RNA levels at Week 96. Of the viruses isolated from subjects experiencing virologic failure on PREZISTA/ritonavir 600/100 mg twice daily (> 7 fold change), 41% were still susceptible to tipranavir and 10% were susceptible to saquinavir while less than 2% were susceptible to the other protease inhibitors (amprenavir, atazanavir, indinavir, lopinavir or nelfinavir).

In Study TMC114-C214, the 7 darunavir/ritonavir virologic failures with reduced susceptibility to darunavir at failure were also resistant to the approved PIs (fos)amprenavir, atazanavir, lopinavir, indinavir, and nelfinavir at failure. Six of these 7 were resistant to saquinavir and 5 were resistant to tipranavir. Four of these virologic failures were already PI-resistant at baseline.

Cross-resistance between darunavir and nucleoside/nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, fusion inhibitors, CCR5 co-receptor antagonists, or integrase inhibitors 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/ritonavir 600/100 mg twice daily therapy. The effect of baseline genotype and phenotype on

virologic response at 96 weeks was analyzed in as-treated analyses using pooled data from the Phase 2b studies (Studies TMC114-C213, TMC114-C202, and TMC114-C215) (n=439). The findings were confirmed with additional genotypic and phenotypic data from the control arms of etravirine Studies TMC125-C206 and TMC125-C216 at Week 24 (n=591).

Diminished virologic responses were observed in subjects with 5 or more baseline IAS-defined primary protease inhibitor resistance-associated substitutions (D30N, V32I, L33F, M46I/L, I47A/V, G48V, I50L/V, I54L/M, L76V, V82A/F/L/S/T, I84V, N88S, L90M) (see Table 12).

Table 12: Response to PREZISTA/ritonavir 600/100 mg twice daily by Baseline Number of IAS-Defined Primary PI Resistance-Associated Substitutions: As-treated Analysis of Studies TMC114-C213, TMC114-C202, and TMC114-C215

	Studies TMC114-C213, TMC114-C202, TMC114-C215 < 50 copies/mL at Week 96 N=439		
# IAS-Defined Primary PI Substitutions	**Overall**	**De Novo ENF**	**Re-Used/ No ENF**
All	44% (192/439)	54% (61/112)	40% (131/327)
0 - 4	50% (162/322)	58% (49/85)	48% (113/237)
5	22% (16/74)	47% (9/19)	13% (7/55)
≥ 6	9% (3/32)	17% (1/6)	8% (2/26)

IAS Primary PI Substitutions (2008): D30N, V32I, L33F, M46I/L, I47A/V, G48V, I50L/V, I54L/M, L76V, V82A/F/L/S/T, I84V, N88S, L90M

The presence at baseline of two or more of the substitutions V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V or L89V was associated with a decreased virologic response to PREZISTA/ritonavir. In subjects not taking enfuvirtide de novo, the proportion of subjects achieving viral load < 50 plasma HIV RNA copies/mL at 96 weeks was 59%, 29%, and 12% when the baseline genotype had 0-1, 2 and ≥ 3 of these substitutions, respectively.

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 13. These baseline phenotype groups are based on the select patient populations in the Studies TMC114-C213, TMC114-C202, and TMC114-C215, and are not meant to represent definitive clinical susceptibility breakpoints for PREZISTA/ritonavir. The data are provided to give clinicians information on the likelihood of virologic success based on pre-treatment susceptibility to darunavir.

Table 13: Response (HIV-1 RNA < 50 copies/mL at Week 96) to PREZISTA/ritonavir 600/100 mg twice daily by Baseline Darunavir Phenotype and by Use of Enfuvirtide (ENF): As-treated Analysis of Studies TMC114-C213, TMC114-C202, and TMC114-C215

	Proportion of Subjects with < 50 copies/mL at Week 96 N=417		
Baseline DRV Phenotype	**All**	**De Novo ENF**	**Re-Used/ No ENF**
Overall	175/417 (42%)	61/112 (54%)	131/327 (40%)
0 - 7	148/270 (55%)	44/65 (68%)	104/205 (51%)
> 7 - 20	16/53 (30%)	7/17 (41%)	9/36 (25%)
> 20	11/94 (12%)	6/23 (26%)	5/71 (7%)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis and Mutagenesis

Darunavir was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. Daily doses of 150, 450 and 1000 mg/kg were administered to mice and doses of 50, 150 and 500 mg/kg were administered to rats. A dose-related increase in the incidence of hepatocellular adenomas and carcinomas were observed in males and females of both species as well as an increase in thyroid follicular cell adenomas in male rats. The observed hepatocellular findings in rodents are considered to be of limited relevance to humans. Repeated administration of darunavir to rats caused hepatic microsomal enzyme induction and increased thyroid hormone elimination, which predispose rats, but not humans, to thyroid neoplasms. At the highest tested doses, the systemic exposures to darunavir (based on AUC) were between 0.4- and 0.7-fold (mice) and 0.7- and 1-fold (rats), relative to those observed in humans at the recommended therapeutic doses (600/100 mg twice daily or 800/100 mg once daily).

Darunavir was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* assays including bacterial reserve mutation (Ames), chromosomal aberration in human lymphocytes and *in vivo* micronucleus test in mice.

Impairment of Fertility

No effects on fertility or early embryonic development were observed with darunavir in rats and darunavir has shown no teratogenic potential in mice (in the presence or absence of ritonavir), rats and rabbits.

13.2 Animal Toxicology and/or Pharmacology

In juvenile rats single doses of darunavir (20 mg/kg to 160 mg/kg at ages 5-11 days) or multiple doses of darunavir (40 mg/kg to 1000 mg/kg at age 12 days) caused mortality. The mortalities were associated with convulsions in some of the animals. Within this age range exposures in plasma, liver and brain were dose and age dependent and were considerably greater than those observed in adult rats. These findings were attributed to the ontogeny of the CYP450 liver enzymes involved in the metabolism of darunavir and the immaturity of the blood-brain barrier. No treatment-related mortalities were noted in juvenile rats after a single dose of darunavir at 1000 mg/kg on day 26 of age or after repeat dosing at 500 mg/kg from day 23 to 50 of age. The exposures and toxicity profile in the older animals (day 23 or day 26) were comparable to those observed in adult rats. Due to uncertainties regarding the rate of development of the human blood-brain barrier and liver enzymes, do not administer PREZISTA/ritonavir in pediatric patients below 3 years of age.

14 CLINICAL STUDIES

14.1 Description of Adult Clinical Studies

The evidence of efficacy of PREZISTA/ritonavir is based on the analyses of 96-week data from 2 randomized, controlled open-label Phase 3 trials in treatment-naïve (TMC114-C211) and antiretroviral treatment-experienced (TMC114-C214) HIV-1-infected adult subjects. In addition, 96-week data is included from 2 randomized, controlled Phase 2b trials, TMC114-C213 and TMC114-C202, in antiretroviral treatment-experienced HIV-1-infected adult subjects.

14.2 Treatment-Naïve Adult Subjects

Study TMC114-C211

Study TMC114-C211 is a randomized, controlled, open-label Phase 3 trial comparing PREZISTA/ritonavir 800/100 mg once daily versus lopinavir/ritonavir 800/200 mg per day (given as a twice daily or as a once daily regimen) in antiretroviral treatment-naïve HIV-1-infected adult subjects. Both arms used a fixed background regimen consisting of tenofovir disoproxil fumarate 300 mg once daily (TDF) and emtricitabine 200 mg once daily (FTC).

HIV-1-infected subjects who were eligible for this trial had plasma HIV-1 RNA $\geq$ 5000 copies/mL. Randomization was stratified by screening plasma viral load (HIV-1 RNA $<$ 100,000 copies/mL or $\geq$ 100,000 copies/mL) and screening CD4+ cell count ($<$ 200 cells/mm^3 or $\geq$ 200 cells/mm^3). Virologic response was defined as a confirmed

plasma HIV-1 RNA viral load < 50 copies/mL. Analyses included 689 subjects in Study TMC114-C211 who had completed 96 weeks of treatment or discontinued earlier.

Demographics and baseline characteristics were balanced between the PREZISTA/ritonavir arm and the lopinavir/ritonavir arm (see Table 14). Table 14 compares the demographic and baseline characteristics between subjects in the PREZISTA/ritonavir 800/100 mg once daily arm and subjects in the lopinavir/ritonavir 800/200 mg per day arm in Study TMC114-C211.

Table 14: Demographic and Baseline Characteristics of Subjects in Study TMC114-C211

	Randomized Study TMC114-C211	
	PREZISTA/ritonavir 800/100 mg once daily + TDF/FTC N = 343	**lopinavir/ritonavir 800/200 mg per day + TDF/FTC N = 346**
Demographic Characteristics		
Median Age (years) (range, years)	34 (18-70)	33 (19-68)
Sex		
Male	70%	70%
Female	30%	30%
Race		
White	40%	45%
Black	23%	21%
Hispanic	23%	22%
Asian	13%	11%
Baseline Characteristics		
Mean Baseline Plasma HIV-1 RNA (log_{10} copies/mL)	4.86	4.84
Median Baseline CD4+ Cell Count (cells/mm^3) (range, cells/mm^3)	228 (4-750)	218 (2-714)
Percentage of Patients with Baseline Viral Load ≥ 100,000 copies/mL	34%	35%
Percentage of Patients with Baseline CD4+ Cell Count < 200 cells/mm^3	41%	43%

Week 96 outcomes for subjects on PREZISTA/ritonavir 800/100 mg once daily from Study TMC114-C211 are shown in Table 15.

Table 15: Virologic Outcome of Randomized Treatment of Study TMC114-C211 at 96 Week Window (Window 90-102 Weeks)

	PREZISTA/ ritonavir 800/100 mg once daily + TDF/FTC N = 343	**lopinavir/ritonavir 800/200 mg per day + TDF/FTC N = 346**
Virologic success HIV-1 RNA < 50 copies/mL	78%	74%
Virologic failure*	11%	12%
No virologic data at Week 96 window		
Reasons		
Discontinued study due to adverse event or death†	4%	9%
Discontinued study for other reasons‡	6%	5%
Missing data during window but on study	1%	< 1%

N = total number of subjects with data

* Includes patients who discontinued prior to Week 96 for lack or loss of efficacy and patients who are ≥ 50 copies in the 96 week window and patients who had a change in their background regimen that was not permitted by the protocol.

† Includes patients who discontinued due to adverse event or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

‡ Other includes: withdrew consent, loss to follow-up, etc., if the viral load at the time of discontinuation was < 50 copies/mL.

In Study TMC114-C211 at 96 weeks of treatment, the median increase from baseline in CD4+ cell counts was 171 cells/mm^3 in the PREZISTA/ritonavir 800/100 mg once daily arm and 188 cells/mm^3 in the lopinavir/ritonavir 800/200 mg per day arm.

14.3 Treatment-Experienced Adult Subjects

Study TMC114-C214

Study TMC114-C214 is a randomized, controlled, open-label Phase 3 trial comparing PREZISTA/ritonavir 600/100 mg twice daily versus lopinavir/ritonavir 400/100 mg twice daily in antiretroviral treatment-experienced, lopinavir/ritonavir-naïve HIV-1-infected adult subjects. Both arms used an optimized background regimen (OBR) consisting of at least 2 antiretrovirals (NRTIs with or without NNRTIs).

HIV-1-infected subjects who were eligible for this trial had plasma HIV-1 RNA > 1000 copies/mL and were on a highly active antiretroviral therapy regimen (HAART) for at least 12 weeks. Virologic response was defined as a confirmed plasma HIV-1 RNA viral load < 400 copies/mL. Analyses included 595 subjects in Study TMC114-C214 who had completed 96 weeks of treatment or discontinued earlier.

Demographics and baseline characteristics were balanced between the PREZISTA/ritonavir arm and the lopinavir/ritonavir arm (see Table 16). Table 16 compares the demographic and baseline characteristics between

subjects in the PREZISTA/ritonavir 600/100 mg twice daily arm and subjects in the lopinavir/ritonavir 400/100 mg twice daily arm in Study TMC114-C214.

Table 16: Demographic and Baseline Characteristics of Subjects in Study TMC114-C214		
	Randomized Study TMC114-C214	
	PREZISTA/ritonavir 600/100 mg twice daily + OBR N = 298	**lopinavir/ritonavir 400/100 mg twice daily + OBR N = 297**
Demographic Characteristics		
Median Age (years) (range, years)	40 (18-68)	41 (22-76)
Sex		
Male	77%	81%
Female	23%	19%
Race		
White	54%	57%
Black	18%	17%
Hispanic	15%	15%
Asian	9%	9%
Baseline Characteristics		
Mean Baseline Plasma HIV-1 RNA (log_{10} copies/mL)	4.33	4.28
Median Baseline CD4+ Cell Count (cells/mm^3) (range, cells/mm^3)	235 (3-831)	230 (2-1096)
Percentage of Patients with Baseline Viral Load ≥ 100,000 copies/mL	19%	17%
Percentage of Patients with Baseline CD4+ Cell Count < 200 cells/mm^3	40%	40%
Median Darunavir Fold Change (range)	0.60 (0.10-37.40)	0.60 (0.1-43.8)
Median Lopinavir Fold Change (range)	0.70 (0.40-74.40)	0.80 (0.30-74.50)
Median Number of Resistance-Associated*: PI mutations NNRTI mutations NRTI mutations	 4 1 2	 4 1 2
Percentage of Subjects with Number of Baseline Primary Protease Inhibitor Mutations*: ≤ 1 2 ≥ 3	 78% 8% 13%	 80% 9% 11%
Median Number of ARVs Previously Used†: NRTIs NNRTIs PIs (excluding low-dose ritonavir)	 4 1 1	 4 1 1
Percentage of Subjects Resistant‡ to All Available§ PIs at Baseline, excluding Darunavir	2%	3%
* Johnson VA, Brun-Vezinet F, Clotet B, et al. Update of the drug resistance mutations in HIV-1: Fall 2006. Top		

HIV Med 2006; 14(3): 125-130
† Only counting ARVs, excluding low-dose ritonavir
‡ Based on phenotype (Antivirogram™)
§ Commercially available PIs at the time of study enrollment

Week 96 outcomes for subjects on PREZISTA/ritonavir 600/100 mg twice daily from Study TMC114-C214 are shown in Table 17.

Table 17: Virologic Outcome of Randomized Treatment of Study TMC114-C214 at 96 Week Window (Window 90-102 Weeks)

	PREZISTA /ritonavir 600/100 mg twice daily + OBR N = 298	**lopinavir/ritonavir 400/100 mg twice daily + OBR N = 297**
Virologic success HIV-1 RNA < 50 copies/mL	58%	52%
Virologic failure*	26%	33%
No virologic data at Week 96 window		
Reasons		
Discontinued study due to adverse event or death†	7%	8%
Discontinued study for other reasons‡	8%	7%
Missing data during window but on study	1%	< 1%

N = total number of subjects with data
* Includes patients who discontinued prior to Week 96 for lack or loss of efficacy and patients who are ≥ 50 copies in the 96 week window and patients who had a change in their OBR that was not permitted by the protocol.
† Includes patients who discontinued due to adverse event or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
‡ Other includes: withdrew consent, loss to follow-up, etc., if the viral load at the time of discontinuation was < 50 copies/mL.

In Study TMC114-C214 at 96 weeks of treatment, the median increase from baseline in CD4+ cell counts was 81 cells/mm^3 in the PREZISTA/ritonavir 600/100 mg twice daily arm and 93 cells/mm^3 in the lopinavir/ritonavir 400/100 mg twice daily arm.

Studies TMC114-C213 and TMC114-C202

Studies TMC114-C213 and TMC114-C202 are randomized, controlled, Phase 2b trials in adult subjects with a high level of PI resistance consisting of 2 parts: an initial partially-blinded, dose-finding part and a second long-term part in which all subjects randomized to PREZISTA/ritonavir received the recommended dose of 600/100 mg twice daily.

HIV-1-infected subjects who were eligible for these trials had plasma HIV-1 RNA > 1000 copies/mL, had prior treatment with PI(s), NNRTI(s) and NRTI(s), had at least one primary PI mutation (D30N, M46I/L, G48V, I50L/V, V82A/F/S/T, I84V, L90M) at screening, and were on a stable PI-containing regimen at screening for at least 8 weeks. Randomization was stratified by the number of PI mutations, screening viral load, and the use of enfuvirtide.

The virologic response rate was evaluated in subjects receiving PREZISTA/ritonavir plus an OBR versus a control group receiving an investigator-selected PI(s) regimen plus an OBR. Prior to randomization, PI(s) and OBR were selected by the investigator based on genotypic resistance testing and prior ARV history. The OBR consisted of at least 2 NRTIs with or without enfuvirtide. Selected PI(s) in the control arm included: lopinavir in 36%, (fos)amprenavir in 34%, saquinavir in 35% and atazanavir in 17%; 98% of control subjects received a ritonavir boosted PI regimen out of which 23% of control subjects used dual-boosted PIs. Approximately 47% of all subjects used enfuvirtide, and 35% of the use was in subjects who were ENF-naïve. Virologic response was defined as a decrease in plasma HIV-1 RNA viral load of at least 1 $\log_{10}$ versus baseline.

In the pooled analysis for TMC114-C213 and TMC114-C202, demographics and baseline characteristics were balanced between the PREZISTA/ritonavir arm and the comparator PI arm (see Table 18). Table 18 compares the demographic and baseline characteristics between subjects in the PREZISTA/ritonavir 600/100 mg twice daily arm and subjects in the comparator PI arm in the pooled analysis of Studies TMC114-C213 and TMC114-C202.

Table 18: Demographic and Baseline Characteristics of Subjects in the Studies TMC114-C213 and TMC114-C202 (Pooled Analysis)

	Randomized Studies TMC114-C213 and TMC114-C202	
	PREZISTA/ritonavir 600/100 mg twice daily + OBR N = 131	**Comparator PI(s) + OBR N = 124**
Demographic Characteristics		
Median Age (years) (range, years)	43 (27-73)	44 (25-65)
Sex		
Male	89%	88%
Female	11%	12%
Race		
White	81%	73%
Black	10%	15%
Hispanic	7%	8%
Baseline Characteristics		
Mean Baseline Plasma HIV-1 RNA ($\log_{10}$ copies/mL)	4.61	4.49
Median Baseline CD4+ Cell Count (cells/mm^3) (range, cells/mm^3)	153 (3-776)	163 (3-1274)
Percentage of Patients with Baseline Viral Load > 100,000 copies/mL	24%	29%
Percentage of Patients with Baseline CD4+ Cell Count < 200 cells/mm^3	67%	58%
Median Darunavir Fold Change	4.3	3.3
Median Number of Resistance-Associated*:		
PI mutations	12	12
NNRTI mutations	1	1
NRTI mutations	5	5
Percentage of Subjects with Number of Baseline Primary Protease Inhibitor Mutations*:		
≤ 1	8%	9%
2	22%	21%
≥ 3	70%	70%

Median Number of ARVs Previously Used†: NRTIs	6	6
NNRTIs	1	1
PIs (excluding low-dose ritonavir)	5	5
Percentage of Subjects Resistant† to All Available‡ PIs at Baseline, excluding Tipranavir and Darunavir	63%	61%
Percentage of Subjects with Prior Use of Enfuvirtide	20%	17%

* Johnson VA, Brun-Vezinet F, Clotet B, et al. Update of the drug resistance mutations in HIV-1: Fall 2006. Top HIV Med 2006; 14(3): 125-130
† Based on phenotype (Antivirogram™)
‡ Commercially available PIs at the time of study enrollment

Week 96 outcomes for subjects on the recommended dose PREZISTA/ritonavir 600/100 mg twice daily from the pooled Studies TMC114-C213 and TMC114-C202 are shown in Table 19.

Table 19: Outcomes of Randomized Treatment Through Week 96 of the Studies TMC114-C213 and TMC114-C202 (Pooled Analysis)

	Randomized Studies TMC114-C213 and TMC114-C202	
	PREZISTA/ritonavir 600/100 mg twice daily + OBR N=131	**Comparator PI + OBR N=124**
Virologic Responders confirmed at least 1 $\log_{10}$ HIV-1 RNA below baseline through Week 96 (< 50 copies/mL at Week 96)	57% (39%)	10% (9%)
Virologic failures	29%	80%
Lack of initial response*	8%	53%
Rebounder†	17%	19%
Never Suppressed‡	4%	8%
Death or discontinuation due to adverse events	9%	3%
Discontinuation due to other reasons	5%	7%

* Subjects who did not achieve at least a confirmed 0.5 $\log_{10}$ HIV-1 RNA drop from baseline at Week 12
† Subjects with an initial response (confirmed 1 $\log_{10}$ drop in viral load), but without a confirmed 1 $\log_{10}$ drop in viral load at Week 96
‡ Subjects who never reached a confirmed 1 $\log_{10}$ drop in viral load before Week 96

In the pooled Studies TMC114-C213 and TMC114-C202 through 48 weeks of treatment, the proportion of subjects with HIV-1 RNA < 400 copies/mL in the arm receiving PREZISTA/ritonavir 600/100 mg twice daily compared to the comparator PI arm was 55.0% and 14.5%, respectively. In addition, the mean changes in plasma HIV-1 RNA from baseline were –1.69 $\log_{10}$ copies/mL in the arm receiving PREZISTA/ritonavir 600/100 mg twice daily and –0.37 $\log_{10}$ copies/mL for the comparator PI arm. The mean increase from baseline in CD4+ cell counts was higher in the arm receiving PREZISTA/ritonavir 600/100 mg twice daily (103 cells/mm^3) than in the comparator PI arm (17 cells/mm^3).

14.4 Pediatric Patients

The pharmacokinetic profile, safety and antiviral activity of PREZISTA/ritonavir were evaluated in a randomized, open-label, multicenter study. This study enrolled treatment-experienced pediatric subjects between the ages of 6 and < 18 years and weighing at least 44 lbs (20 kg). Patients were stratified according to their weight (≥ 20 - < 30 kg, ≥ 30 - < 40 kg, ≥ 40 kg) and received PREZISTA/ritonavir plus background therapy consisting of at least two non-protease inhibitor antiretroviral drugs. Eighty patients were randomized and received at least one dose of PREZISTA/ritonavir. Pediatric subjects who were at risk of discontinuing therapy due to intolerance of ritonavir oral solution (e.g., taste aversion) were allowed to switch to the capsule formulation. Of the 44 pediatric subjects taking ritonavir oral solution, 23 subjects switched to the 100 mg capsule formulation and exceeded the weight-based ritonavir dose without changes in observed safety.

The 80 randomized pediatric subjects had a median age of 14 (range 6 - < 18 years), and were 71% male, 54% Caucasian, 30% Black, 9% Hispanic and 8% other. The mean baseline plasma HIV-1 RNA was 4.64 $\log_{10}$ copies/mL, and the median baseline CD4+ cell count was 330 cells/mm^3 (range: 6 to 1505 cells/mm^3). Overall, 38% of pediatric subjects had baseline plasma HIV-1 RNA ≥ 100,000 copies/mL. Most pediatric subjects (79%) had previous use of at least one NNRTI and 96% of pediatric subjects had previously used at least one PI.

Seventy-seven pediatric subjects (96%) completed the 24 week period. Of the patients who discontinued, one patient discontinued treatment due to an adverse event. An additional 2 patients discontinued for other reasons, one patient due to compliance and another patient due to relocation.

The proportion of pediatric subjects with HIV-1 RNA < 400 copies/mL and < 50 copies/mL was 64% and 50%, respectively. The mean CD4+ cell count increase from baseline was 117 cells/mm^3.

The dose selection was based on the following:

- Similar darunavir plasma exposures in children compared to adults
- Similar virologic response rates and safety profile in children compared to adults

16 HOW SUPPLIED/STORAGE AND HANDLING

PREZISTA (darunavir) 75 mg tablets are supplied as white, caplet-shaped, film-coated tablets containing darunavir ethanolate equivalent to 75 mg of darunavir per tablet. Each tablet is debossed with “75” on one side and “TMC” on the other side.

PREZISTA (darunavir) 150 mg tablets are supplied as white, oval-shaped, film-coated tablets containing darunavir ethanolate equivalent to 150 mg of darunavir per tablet. Each tablet is debossed with “150” on one side and “TMC” on the other side.

PREZISTA (darunavir) 300 mg tablets are supplied as orange, oval-shaped, film-coated tablets containing darunavir ethanolate equivalent to 300 mg of darunavir per tablet. Each tablet is debossed with “300” on one side and “TMC114” on the other side.

PREZISTA (darunavir) 400 mg tablets are supplied as light orange, oval-shaped, film-coated tablets containing darunavir ethanolate equivalent to 400 mg of darunavir per tablet. Each tablet is debossed with “400” on one side and “TMC” on the other side.

PREZISTA (darunavir) 600 mg tablets are supplied as orange, oval-shaped, film-coated tablets containing darunavir ethanolate equivalent to 600 mg of darunavir per tablet. Each tablet is debossed with “600” on one side and “TMC” on the other side.

PREZISTA tablets are packaged in bottles in the following configuration:

75 mg tablets—bottles of 480 (NDC 59676-563-01)
150 mg tablets—bottles of 240 (NDC 59676-564-01)
300 mg tablets—bottles of 120 (NDC 59676-560-01)
400 mg tablets—bottles of 60 (NDC 59676-561-01)

600 mg tablets—bottles of 60 (NDC 59676-562-01)

Storage:
Store PREZISTA tablets at 25°C (77°F); with excursions permitted to 15°-30°C (59°-86°F).

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling]

A statement to patients and healthcare providers is included on the product's bottle label: **ALERT: Find out about medicines that should NOT be taken with PREZISTA.** A Patient Package Insert for PREZISTA is available for patient information.

17.1 General

Patients should be informed that PREZISTA is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. Patients should be told that there are currently no data demonstrating that therapy with PREZISTA can reduce the risk of transmitting HIV to others.

Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician while using PREZISTA.

17.2 Instructions for Use

General

Patients should be advised to take PREZISTA and ritonavir (NORVIR®) with food every day as prescribed. Patients should be instructed to swallow whole tablets with a drink such as water or milk. PREZISTA must always be used with ritonavir (NORVIR®) in combination with other antiretroviral drugs. Patients should not alter the dose of either PREZISTA or ritonavir (NORVIR®), discontinue ritonavir (NORVIR®), or discontinue therapy with PREZISTA without consulting their physician.

Patients Taking PREZISTA Once Daily

If a patient misses a dose of PREZISTA or ritonavir (NORVIR®) by more than 12 hours, the patient should be told to wait and then take the next dose of PREZISTA and ritonavir (NORVIR®) at the regularly scheduled time. If the patient misses a dose of PREZISTA or ritonavir (NORVIR®) by less than 12 hours, the patient should be told to take PREZISTA and ritonavir (NORVIR®) immediately, and then take the next dose of PREZISTA and ritonavir (NORVIR®) at the regularly scheduled time. If a dose of PREZISTA or ritonavir (NORVIR®) is skipped, the patient should not double the next dose. Inform the patient that he or she should not take more or less than the prescribed dose of PREZISTA or ritonavir (NORVIR®).

Patients Taking PREZISTA Twice Daily

If a patient misses a dose of PREZISTA or ritonavir (NORVIR®) by more than 6 hours, the patient should be told to wait and then take the next dose of PREZISTA and ritonavir (NORVIR®) at the regularly scheduled time. If the patient misses a dose of PREZISTA or ritonavir (NORVIR®) by less than 6 hours, the patient should be told to take PREZISTA and ritonavir (NORVIR®) immediately, and then take the next dose of PREZISTA and ritonavir (NORVIR®) at the regularly scheduled time. If a dose of PREZISTA or ritonavir (NORVIR®) is skipped, the patient should not double the next dose. Inform the patient that he or she should not take more or less than the prescribed dose of PREZISTA or ritonavir (NORVIR®).

17.3 Drug Interactions

PREZISTA/ritonavir may interact with many drugs; therefore, patients should be advised to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including St. John's wort.

Patients receiving estrogen-based contraceptives should be instructed to use alternate contraceptive measures during therapy with PREZISTA/ritonavir because hormonal levels may decrease.

17.4 Fat Redistribution

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, including PREZISTA/ritonavir, and that the cause and long-term health effects of these conditions are not known at this time.

Manufactured for Tibotec, Inc. by:
JOLLC, Gurabo, Puerto Rico
Distributed by:
Tibotec Therapeutics, Division of Centocor Ortho Biotech Products, L.P., Raritan NJ 08869

Patent Numbers: 5,843,946; 6,248,775; 6,335,460 and other US patents pending

FDA-Approved Patient Labeling

PREZISTA® (darunavir) Tablets

Patient Information about
PREZISTA (pre-ZIS-ta)
for HIV (Human Immunodeficiency Virus) Infection
Generic name: darunavir (da-ROO-nuh-veer)

ALERT: Find out about medicines that should NOT be taken with PREZISTA. Please also read the section "Who should not take PREZISTA?".

Please read this information before you start taking PREZISTA. Also, read the leaflet each time you renew your prescription, just in case anything has changed. Remember, this leaflet does not take the place of careful discussions with your doctor. You and your doctor should discuss your treatment with PREZISTA prior to the first time you take your medicine and at regular checkups. You should remain under a doctor's care when using PREZISTA and should not change or stop treatment without first talking with a doctor.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT PREZISTA?

PREZISTA, together with NORVIR® (ritonavir), has rarely been observed to cause liver problems which may be life-threatening. It was not always clear if PREZISTA caused these liver problems because some patients had other illnesses or were taking other medicines. Your healthcare professional should do blood tests prior to initiating combination treatment including PREZISTA. If you have chronic hepatitis B or C infection, your healthcare professional should check your blood tests more often because you have an increased chance of developing liver problems. Please also read the section "What are the possible side effects of PREZISTA?".

Rarely, PREZISTA has been reported to cause a severe or life-threatening rash. Contact your healthcare provider immediately if you develop a rash. Your healthcare provider will advise you whether your symptoms can be managed on therapy or whether PREZISTA should be stopped.

WHAT IS PREZISTA?

PREZISTA is an oral tablet used for the treatment of HIV (Human Immunodeficiency Virus) infection in adults and children 6 years of age and older. HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome). PREZISTA is a type of anti-HIV medicine called a protease (PRO-tee-ase) inhibitor.

HOW DOES PREZISTA WORK?

PREZISTA blocks HIV protease, an enzyme which is needed for HIV to multiply. When used with other anti-HIV medicines, PREZISTA can help to reduce the amount of HIV in your blood (called "viral load") and increase your CD4 (T) cell count. HIV infection destroys CD4 (T) cells, which are important to the immune system. The immune system helps fight infection. Reducing the amount of HIV and increasing the CD4 (T) cell count may improve your immune system and, thus, reduce the risk of death or infections that can happen when your immune system is weak (opportunistic infections).

PREZISTA is always taken with and at the same time as ritonavir (NORVIR®), in combination with other anti-HIV medicines. PREZISTA should also be taken with food.

DOES PREZISTA CURE HIV OR AIDS?

PREZISTA does **not** cure HIV infection or AIDS. At present, there is no cure for HIV infection. People taking PREZISTA may still develop infections or other conditions associated with HIV infection. Because of this, it is very important for you to remain under the care of a doctor. Although PREZISTA is not a cure for HIV or AIDS, PREZISTA can help reduce your risks of getting illnesses associated with HIV infection (AIDS and opportunistic infection) and eventually dying from these conditions.

DOES PREZISTA REDUCE THE RISK OF PASSING HIV TO OTHERS?

PREZISTA does **not** reduce the risk of passing HIV to others through sexual contact, sharing needles, or being exposed to your blood. For your health and the health of others, it is important to always practice safer sex by using a latex or polyurethane condom or other barrier method to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood. Never re-use or share needles.

Ask your doctor if you have any questions on how to prevent passing HIV to other people.

WHAT SHOULD I TELL MY DOCTOR BEFORE I TAKE PREZISTA?

Tell your doctor about all of your medical conditions, including if you:

- are allergic to sulfa medicines.
- have diabetes. In general, anti-HIV medicines, such as PREZISTA, might increase sugar levels in the blood.
- have liver problems, including hepatitis B and/or C.
- have hemophilia. Anti-HIV medicines, such as PREZISTA, might increase the risk of bleeding.
- are pregnant or planning to become pregnant. The effects of PREZISTA on pregnant women or their unborn babies are not known. You and your doctor will need to decide if taking PREZISTA is right for you. If you take PREZISTA while you are pregnant, talk to your doctor about how you can be included in the Antiretroviral Pregnancy Registry.
- are breastfeeding. Do not breastfeed if you are taking PREZISTA. You should not breastfeed if you have HIV because of the chance of passing HIV to your baby. Talk with your doctor about the best way to feed your baby.

WHO SHOULD NOT TAKE PREZISTA?[**]

Together with your doctor, you need to decide whether taking PREZISTA is right for you.

Do not take or administer PREZISTA:

- to children younger than 6 years of age
- if you are or your child is allergic to darunavir or any of the other ingredients in PREZISTA
- if you are or your child is allergic to ritonavir (NORVIR®)
- if you take or your child takes any of the following types of medicines because you could experience serious side effects:

Type of Drug	Examples of Generic Names (Brand Names)
Alpha 1-adrenoreceptor antagonist	alfuzosin (Uroxatral®)
Ergot Derivatives (to treat migraine and headaches)	dihydroergotamine (D.H.E. 45®, Migranal®) ergonovine ergotamine (Cafergot®, Ergomar®) methylergonovine
Gastrointestinal Motility Agent (to treat some digestive conditions)	cisapride
Neuroleptic (to treat psychiatric conditions)	pimozide (Orap®)

[**] The brands listed are the registered trademarks of their respective owners and are not trademarks of Tibotec Pharmaceuticals

Sedative/hypnotics (to treat trouble with sleeping and/or anxiety)	oral midazolam triazolam (Halcion®)
Herbal Product	St. John's wort (*Hypericum perforatum*)
HMG-CoA Reductase Inhibitors (also known as statins) (to lower cholesterol levels)	lovastatin (Mevacor®, Altoprev®, Advicor®) simvastatin (Zocor®, Simcor®, Vytorin®)
Antimycobacterial (to treat tuberculosis or *Mycobacterium avium* complex)	rifampin (Rifadin®, Rifater®, Rifamate®, Rimactane®)
PDE-5 inhibitor (to treat pulmonary arterial hypertension)	sildenafil (Revatio®)

CAN PREZISTA BE TAKEN WITH OTHER MEDICATIONS?**

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins, and herbal supplements. PREZISTA and many other medicines can interact. Sometimes serious side effects will happen if PREZISTA is taken with certain other medicines (see "Who should not take PREZISTA?").

Tell your doctor if you are taking estrogen-based contraceptives (birth control). PREZISTA might reduce the effectiveness of estrogen-based contraceptives. You must take additional precautions for birth control such as a condom.
Tell your doctor if you take other anti-HIV medicines. PREZISTA can be combined with some other anti-HIV medicines while other combinations are not recommended.

Tell your doctor if you are taking any of the following medicines:

Type of Drug	Examples of Generic Names (Brand Names)
Antiarrhythmics (to treat abnormal heart rhythms)	bepridil lidocaine quinidine amiodarone (Cordarone®) digoxin (Lanoxin®) flecainide (Tambocor®) propafenone (Rythmol®)
Anticoagulants (to treat and prevent blood clots)	warfarin (Coumadin®)
Anticonvulsants (to treat epilepsy and prevent seizures)	carbamazepine (Tegretol®, Carbatrol®) phenobarbital phenytoin (Dilantin®, Phenytek®)
Antidepressants (to treat depression)	trazodone (Desyrel®) desipramine (Norpramin®)
Antigout (to treat gout and familial Mediterranean fever)	colchicine (Colcrys®)

** The brands listed are the registered trademarks of their respective owners and are not trademarks of Tibotec Pharmaceuticals

Type of Drug	Examples of Generic Names (Brand Names)
Anti-infectives (to treat bacterial infections)	clarithromycin (Biaxin®)
Antifungals (to treat fungal infections)	ketoconazole (Nizoral®) itraconazole (Sporanox®) voriconazole (Vfend®)
Antimycobacterials (to treat tuberculosis or *Mycobacterium avium* complex)	rifabutin (Mycobutin®)
β-Blockers (to treat high blood pressure, heart attack, or heart failure or to lower pressure in the eye)	metoprolol (Lopressor®, Toprol-XL®) timolol (Betimol®, Combigan®, Istalol®, Cosopt®, Timoptic®)
Benzodiazepines (to treat anxiety and/or trouble with sleeping)	midazolam administered by injection
Calcium Channel Blockers (to treat heart disease)	felodipine (Plendil®) nifedipine (Adalat®) nicardipine (Cardene®)
Corticosteroids (to treat inflammation or asthma)	dexamethasone fluticasone (Advair Diskus®, Cutivate®, Flonase®, Flovent Diskus®)
Endothelin receptor antagonist (to treat pulmonary arterial hypertension)	bosentan (Tracleer®)
HMG-CoA Reductase Inhibitors (also known as statins) (to lower cholesterol levels)	atorvastatin (Lipitor®) pravastatin (Pravachol®) rosuvastatin (Crestor®)
Immunosuppressants (to prevent organ transplant rejection)	cyclosporine (Sandimmune®, Neoral®) tacrolimus (Prograf®) sirolimus (Rapamune®)
Inhaled beta agonist	salmeterol (Serevent®)
Narcotic Analgesics/Treatment of Opioid Dependence (to treat narcotic withdrawal and dependence)	methadone buprenorphine/naloxone
Neuroleptics (to treat schizophrenia or bipolar disorder)	risperidone (Risperdal®, Risperdal® Consta®, Risperdal® M-TAB®) thioridazine
PDE-5 Inhibitors (to treat erectile dysfunction)	sildenafil (Viagra®) vardenafil (Levitra®) tadalafil (Cialis®)
PDE-5 Inhibitors (to treat pulmonary arterial hypertension)	tadalafil (Adcirca®)
Selective Serotonin Reuptake Inhibitors (SSRIs) (to treat depression, anxiety, or panic disorder)	paroxetine (Paxil®) sertraline (Zoloft®)

Tell your doctor if you are taking any medicines that you obtained without a prescription.

This is **not** a complete list of medicines that you should tell your doctor that you are taking. Know and keep track of all the medicines you take and have a list of them with you. Show this list to all of your doctors and pharmacists any time you get a new medicine. Both your doctor and your pharmacist can tell you if you can take these other medicines with PREZISTA. Do not start any new medicines while you are taking PREZISTA without first talking with your doctor or pharmacist. You can ask your doctor or pharmacist for a list of medicines that can interact with PREZISTA.

HOW SHOULD I TAKE PREZISTA?

Take PREZISTA tablets every day exactly as prescribed by your doctor. You must take ritonavir (NORVIR®) at the same time as PREZISTA.

- For adults who have never taken anti-HIV medicines, the usual dose is 800 mg (two 400 mg tablets) of PREZISTA, together with 100 mg (one 100 mg capsule) of ritonavir (NORVIR®), once daily *every day*.
- For adults who have taken anti-HIV medicines in the past, the usual dose is 600 mg (one 600 mg tablet or two 300 mg tablets) of PREZISTA, together with 100 mg (one 100 mg capsule) of ritonavir (NORVIR®), twice daily *every day*. Do not take PREZISTA once daily if you have taken anti-HIV medicines in the past.
- For children at least 6 years of age weighing at least 44 lbs (20 kg), your child's doctor will decide the right dose based on your child's weight. Your child's doctor will inform you exactly on how many PREZISTA tablets and how much ritonavir (NORVIR®) (capsules or solution) your child should take. In case your child does not tolerate ritonavir oral solution, ask your child's doctor for advice. Do not give PREZISTA once daily to your child.

PREZISTA and ritonavir (NORVIR®) should be taken together at the same time every day. If you have questions about when to take PREZISTA and ritonavir (NORVIR®), your doctor can help you decide which schedule works for you.

Take PREZISTA and ritonavir (NORVIR®) **with food.** Swallow the whole tablets with a drink such as water or milk. Do not chew the tablets.

Continue taking PREZISTA and ritonavir (NORVIR®) unless your doctor tells you to stop. Take the exact amount of PREZISTA and ritonavir (NORVIR®) that your doctor tells you to take, right from the very start. To help make sure you will benefit from PREZISTA and ritonavir (NORVIR®), you must not skip doses or interrupt therapy. If you don't take PREZISTA and ritonavir (NORVIR®) as prescribed, the beneficial effects of PREZISTA and ritonavir (NORVIR®) may be reduced or even lost.

Patients taking PREZISTA once daily

If you miss a dose of PREZISTA or ritonavir (NORVIR®) by more than 12 hours, wait and then take the next dose of PREZISTA and ritonavir (NORVIR®) at the regularly scheduled time. If you miss a dose of PREZISTA or ritonavir (NORVIR®) by less than 12 hours, take your missed dose of PREZISTA and ritonavir (NORVIR®) immediately. Then take your next dose of PREZISTA and ritonavir (NORVIR®) at the regularly scheduled time.

Patients taking PREZISTA twice daily

If you miss a dose of PREZISTA or ritonavir (NORVIR®) by more than 6 hours, wait and then take the next dose of PREZISTA and ritonavir (NORVIR®) at the regularly scheduled time. If you miss a dose of PREZISTA or ritonavir (NORVIR®) by less than 6 hours, take your missed dose of PREZISTA and ritonavir (NORVIR®) immediately. Then take your next dose of PREZISTA and ritonavir (NORVIR®) at the regularly scheduled time.

You should always take PREZISTA and ritonavir (NORVIR®) together with food.

If a dose of PREZISTA or ritonavir (NORVIR®) is skipped, do not double the next dose. Do not take more or less than your prescribed dose of PREZISTA or ritonavir (NORVIR®) at any one time.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF PREZISTA?

Like all prescription drugs, PREZISTA can cause side effects. The following is **not** a complete list of side effects reported with PREZISTA when taken either alone or with other anti-HIV medicines. Do not rely on this leaflet alone for information about side effects. Your doctor can discuss with you a more complete list of side effects.

PREZISTA, together with NORVIR® (ritonavir), has rarely been observed to cause liver problems which may be life-threatening. It was not always clear if PREZISTA caused these liver problems because some patients had other illnesses or were taking other medicines. Your healthcare professional should do blood tests prior to initiating combination treatment including PREZISTA. If you have chronic hepatitis B or C infection, your healthcare professional should check your blood tests more often because you have an increased chance of developing liver problems.

Talk to your healthcare professional about the signs and symptoms of liver problems. These may include yellowing of your skin or whites of your eyes, dark (tea colored) urine, pale colored stools (bowel movements), nausea, vomiting, loss of appetite, or pain, aching or sensitivity on your right side below your ribs.

Rash has been reported in 10.3% of patients receiving PREZISTA. In few patients, PREZISTA has been reported to cause a severe or life-threatening rash. Contact your healthcare provider immediately if you develop a rash. Your healthcare provider will advise you whether your symptoms can be managed on therapy or whether PREZISTA should be stopped.

Other relevant severe side effects reported at an uncommon or rare frequency were inflammation of the liver or pancreas, increased blood fat levels, diabetes, and changes in body fat.

Some side effects are typical for anti-HIV medicines in the same family as PREZISTA. These are:

- high blood sugar (hyperglycemia) and diabetes. This can happen in patients taking PREZISTA or other protease inhibitor medicines. Some patients have diabetes before starting treatment with PREZISTA which gets worse. Some patients get diabetes during treatment with PREZISTA. Some patients will need changes in their diabetes medicine. Some patients may need new diabetes medicine.
- increased bleeding in patients with hemophilia.
- changes in body fat. These changes can happen in patients taking anti-HIV medicines, including PREZISTA. The changes may include an increased amount of fat in the upper back and neck, breast, and around the back, chest, and stomach area. Loss of fat from the legs, arms, and face may also happen. The exact cause and long-term health effects of these conditions are not known.
- immune reconstitution syndrome. In some patients with advanced HIV infection (AIDS) and a history of opportunistic infection, signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment, including PREZISTA, is started. It is believed that these symptoms are due to an improvement in the body's immune response, enabling the body to fight infections that may have been present with no obvious symptoms.

The most common side effects include diarrhea, nausea, rash, headache, abdominal pain and vomiting.

Tell your doctor promptly about these or any other unusual symptoms. If the condition persists or worsens, seek medical attention.

WHAT DO PREZISTA TABLETS LOOK LIKE?

PREZISTA 75 mg tablets are white, caplet-shaped, film-coated tablets mentioning "75" on one side and "TMC" on the other side.

PREZISTA 150 mg tablets are white, oval-shaped, film-coated tablets mentioning "150" on one side and "TMC" on the other side.

PREZISTA 300 mg tablets are orange, oval-shaped, film-coated tablets mentioning "300" on one side and "TMC114" on the other side.

PREZISTA 400 mg tablets are light orange, oval-shaped, film-coated tablets mentioning “400” on one side and “TMC” on the other side.

PREZISTA 600 mg tablets are orange, oval-shaped, film-coated tablets mentioning “600” on one side and “TMC” on the other side.

HOW SHOULD I STORE PREZISTA TABLETS?

Store PREZISTA tablets at room temperature (77°F (25°C)). Short-term exposure to higher or lower temperatures [from 59°F (15°C) to 86°F (30°C)] is acceptable. Ask your doctor or pharmacist if you have any questions about storing your tablets.

This medication is prescribed for your particular condition. Do not use it for any other condition or give it to anybody else. Keep PREZISTA and all of your medicines out of the reach of children. If you suspect that more than the prescribed dose of this medicine has been taken, contact your local poison control center or emergency room immediately.

This leaflet provides a summary of information about PREZISTA. If you have any questions or concerns about either PREZISTA or HIV, talk to your doctor.

For additional information, you may also call Tibotec Therapeutics at 1-877-REACH-TT or 1-877-732-2488.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21976	SUPPL-16	CENTOCOR ORTHO BIOTECH INC	PREZISTA

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/s/

KENDALL A MARCUS
04/26/2010