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

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults

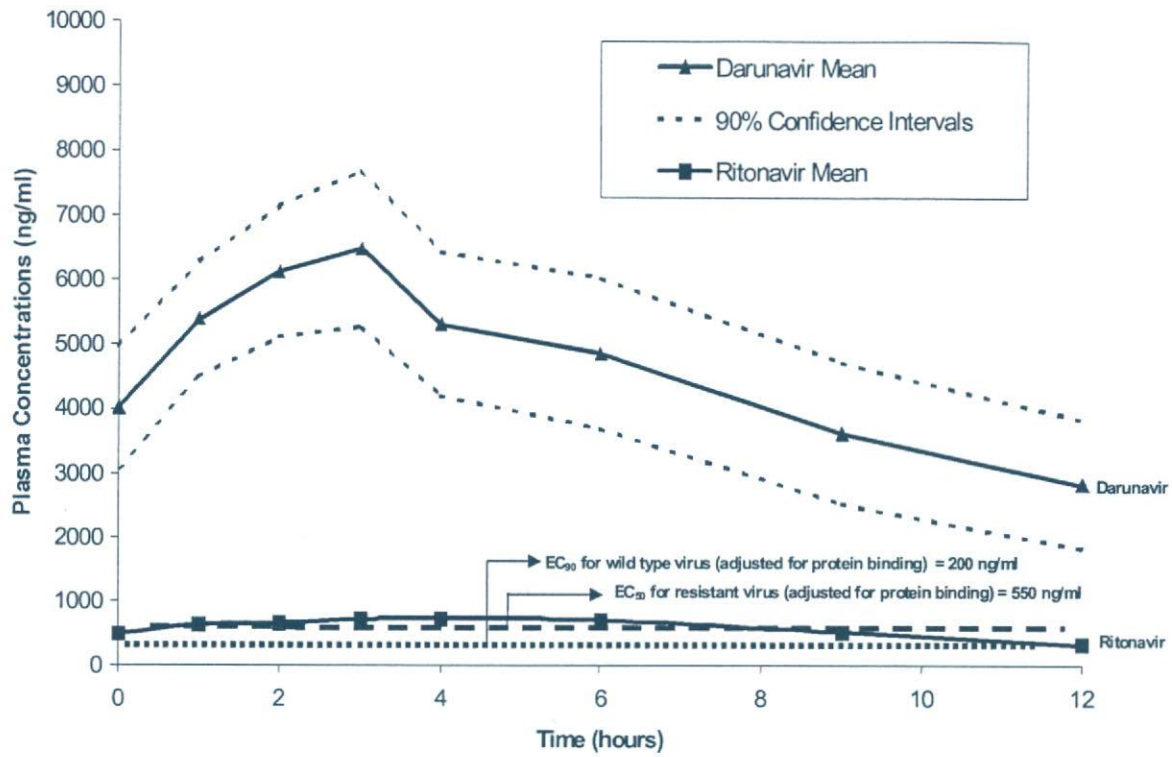
The pharmacokinetics of darunavir, co-administered with low dose ritonavir (100 mg twice daily), have been evaluated in healthy adult volunteers and in HIV-1 infected subjects. Table 3 displays the population pharmacokinetic estimates of darunavir from an analysis of integrated data from Studies TMC114-C213 and TMC114-C202 of 119 subjects administered the darunavir/ritonavir 600/100 mg b.i.d. dose. Darunavir is primarily metabolized by CYP3A. Ritonavir inhibits CYP3A, thereby increasing the plasma concentrations of darunavir. When a single dose of 600 mg darunavir was given orally in combination with 100 mg ritonavir b.i.d., there was an approximate 14-fold increase in the systemic exposure of darunavir. Therefore, PREZISTA should only be used in combination with 100 mg of ritonavir to achieve sufficient exposures of darunavir.

Table 3: Population Pharmacokinetic Estimates of Darunavir at the Darunavir/Ritonavir 600/100 mg b.i.d. dose (Integrated data from TMC114-C213 and TMC114-C202, Primary 24-Week Analysis)

Parameter	**Darunavir/Ritonavir 600/100 mg b.i.d. N = 119**
AUC_{12h} (ng·h/mL)	
Geometric Mean ± Standard Deviation	62349 ± 16143
Median (Range)	61668 (33857-106490)
C_{0h} (ng/mL)	
Geometric Mean ± Standard Deviation	3578 ± 1151
Median (Range)	3539 (1255-7368)
N = number of subjects with data.	

Figure 1 displays the mean plasma concentrations of darunavir and ritonavir at steady-state for the darunavir/ritonavir 600/100 mg b.i.d. dose.

Figure 1: Mean Steady-State Plasma Concentration-Time Profiles of Darunavir and Ritonavir at 600/100 mg b.i.d. at Week 4 (Integrated data from TMC114-C213 and TMC114-C202, Primary 24-Week Analysis)



Absorption and Bioavailability: Darunavir, co-administered with 100 mg ritonavir twice daily, was absorbed following oral administration with a T_{max} of approximately 2.5-4 hours. The absolute oral bioavailability of a single 600 mg dose of darunavir alone and after co-administration with 100 mg ritonavir twice daily was 37% and 82%, respectively.

Effects of Food on Oral Absorption: When administered with food, the C_{max} and AUC of darunavir, co-administered with ritonavir, is approximately 30% higher relative to the fasting state. Therefore, PREZISTA tablets, co-administered with ritonavir, should always be taken with food. Within the range of meals studied, darunavir exposure is similar. The total caloric content of the various meals evaluated ranged from 240 Kcal (12 gms fat) to 928 Kcal (56 gms fat).

Distribution: Darunavir is approximately 95% bound to plasma proteins. Darunavir binds primarily to plasma alpha 1-acid glycoprotein (AAG).

Metabolism: *In vitro* experiments with human liver microsomes (HLMs) indicate that darunavir primarily undergoes oxidative metabolism. Darunavir is extensively metabolized by CYP enzymes, primarily by CYP3A. A mass balance study in healthy volunteers showed that after a single dose administration of 400 mg ^{14}C-darunavir, co-administered with 100 mg ritonavir, the

majority of the radioactivity in the plasma was due to darunavir. At least 3 oxidative metabolites of darunavir have been identified in humans; all showed activity that was at least 90% less than the activity of darunavir against wild-type HIV.

Elimination: A mass balance study in healthy volunteers showed that after single dose administration of 400 mg ^{14}C-darunavir, co-administered with 100 mg ritonavir, approximately 79.5% and 13.9% of the administered dose of ^{14}C-darunavir was recovered in the feces and urine, respectively. Unchanged darunavir accounted for approximately 41.2% and 7.7% of the administered dose in feces and urine, respectively. The terminal elimination half-life of darunavir was approximately 15 hours when combined with ritonavir. After intravenous administration, the clearance of darunavir, administered alone and co-administered with 100 mg twice daily ritonavir, was 32.8 L/h and 5.9 L/h, respectively.

Special Populations

Hepatic Impairment: Darunavir primarily undergoes hepatic metabolism. PREZISTA has not been studied in patients with varying degrees of hepatic impairment (see PRECAUTIONS, *Patients with co-existing conditions*, *Hepatic Impairment* and DOSAGE AND ADMINISTRATION).

Hepatitis B or Hepatitis C Virus Co-infection: The primary 24-week analysis of the data from Study TMC114-C213 in 31 HIV-1 infected subjects indicated that hepatitis B and/or hepatitis C virus co-infection status had no apparent effect on the exposure of darunavir.

Renal Impairment: Results from a mass balance study with ^{14}C-darunavir/ritonavir showed that approximately 7.7% of the administered dose of darunavir is excreted in the urine as unchanged drug. As darunavir and ritonavir are highly bound to plasma proteins, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis. Population pharmacokinetic analysis showed that the pharmacokinetics of darunavir were not significantly affected in HIV infected subjects with moderate renal impairment (CrCL between 30-60 mL/min, n=20). There are no pharmacokinetic data available in HIV-1 infected patients with severe renal impairment or end stage renal disease. (see PRECAUTIONS, *Patients with co-existing conditions*, *Renal Impairment*, and DOSAGE AND ADMINISTRATION).

Gender: Population pharmacokinetic analysis showed higher mean darunavir exposure (16.8%) in HIV infected females (n=68) compared to males. This difference is not clinically relevant.

Race: Population pharmacokinetic analysis of darunavir in HIV infected subjects indicated that race had no apparent effect on the exposure to darunavir.

Geriatric Patients: Population pharmacokinetic analysis in HIV infected subjects showed that darunavir pharmacokinetics are not considerably different in the age range (18 to 75 years) evaluated in HIV infected subjects (n=12, age $\geq$ 65) (see PRECAUTIONS, *Geriatric Use*).

Pediatric Patients: The pharmacokinetics of darunavir in combination with ritonavir in pediatric patients has not been established. There are insufficient data at this time to recommend a dose.

Drug Interactions: See also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS, Drug Interactions.

Darunavir and ritonavir are both inhibitors of CYP3A. Co-administration of darunavir and ritonavir with drugs primarily metabolized by CYP3A may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse events (see sections CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS, *Drug Interactions*).

Darunavir and ritonavir are metabolized by CYP3A. Drugs that induce CYP3A activity would be expected to increase the clearance of darunavir and ritonavir, resulting in lowered plasma concentrations of darunavir and ritonavir. Co-administration of darunavir and ritonavir and other drugs that inhibit CYP3A may decrease the clearance of darunavir and ritonavir and may result in increased plasma concentrations of darunavir and ritonavir.

Drug interaction studies were performed with darunavir and other drugs likely to be co-administered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration of darunavir on the AUC, C_{max}, and C_{min} values are summarized in Table 4 (effect of other drugs on darunavir) and Table 5 (effect of darunavir on other drugs). For information regarding clinical recommendations, see PRECAUTIONS, *Drug Interactions*.

Table 4: 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/ rtv			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.	300/100 mg b.i.d.	9	↓	0.61 (0.51-0.74)	0.47 (0.40-0.55)	0.35 (0.29-0.42)
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							
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)
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							
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)
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. = daily
† b.i.d. = twice daily
‡ Ratio based on between-study comparison.

Table 5:	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/ rtv	N	PK	C_{max}	AUC	C_{min}
Co-Administration With Other Protease Inhibitors							
Atazanavir	300 mg q.d.^ /100 mg RTV 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 RTV 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.	300/100 mg b.i.d.	9	↑	1.22 (1.12-1.32)	1.37 (1.27-1.49)	1.72 (1.46-2.03)
Saquinavir hard gel capsule	1000 mg b.i.d. /100 mg RTV b.i.d. when administered alone 1000 mg b.i.d. when	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)

	administered with darunavir/ ritonavir						
Co-Administration With Other Antiretrovirals							
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)
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)

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)
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)
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)
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)	-
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)	-

N = number of subjects with data;- = no information available.
^ q.d. = daily
† b.i.d. = twice daily

INDICATIONS AND USAGE

PREZISTA, co-administered with 100 mg ritonavir (PREZISTA/rtv), 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/rtv 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/rtv:

- Treatment history and, when available, genotypic or phenotypic testing, should guide the use of PREZISTA/rtv (see MICROBIOLOGY).
- The use of other active agents with PREZISTA/rtv is associated with a greater likelihood of treatment response (see MICROBIOLOGY and INDICATIONS AND USAGE, *Description of Clinical Studies*).
- The risks and benefits of PREZISTA/rtv have not been established in treatment-naïve adult patients or pediatric patients.

Description of Clinical Studies

The evidence of efficacy of PREZISTA/rtv is based on the analyses of 24-week data from 2 ongoing, randomized, controlled trials, TMC114-C213 and TMC114-C202, in antiretroviral treatment-experienced HIV-1 infected adult subjects. These efficacy results were supported by the 24-week pooled analysis of the open label trials TMC114-C215 and TMC114-C208 of subjects who initiated PREZISTA/rtv at the recommended dose.

Treatment-Experienced Subjects:

Studies TMC114-C213 and TMC114-C202: These are ongoing randomized, controlled, Phase 2b trials consisting of 2 parts: an initial partially-blinded, dose-finding part and a second long-term part in which all subjects randomized to PREZISTA/rtv received the recommended dose of 600/100 mg b.i.d.

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.

Analyses included 318 subjects in Study TMC114-C213 and 319 subjects in Study TMC114-C202 who had completed 24 weeks of treatment or discontinued earlier.

At 24 weeks, the virologic response rate was evaluated in subjects receiving PREZISTA/rtv plus an optimized background regimen (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/ritonavir in 36%, (fos)amprenavir in 34%, saquinavir in 35% and atazanavir in 17%; 23% of the 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 1.0 $\log_{10}$ versus baseline.

In the pooled analysis for TMC114-C213 and TMC114-C202, demographics and baseline characteristics were balanced between the PREZISTA/rtv arm and the comparator PI arm. Table 6 compares the demographic characteristics between subjects in the PREZISTA/rtv 600/100 mg b.i.d. arm and subjects in the comparator PI arm.

Table 6: Demographic Characteristics of Subjects in the Studies TMC114-C213 and TMC114-C202 (Pooled Analysis)

	Randomized Studies TMC114-C213 and TMC114-C202	
	PREZISTA/rtv 600/100 mg b.i.d. + OBR N = 131	Comparator PI(s) + OBR N = 124
Demographic Characteristics		
Age (years) (range, years)	43.0 (27-73)	44.0 (25-65)
Sex		
Male	89%	88%
Female	11%	12%
Race		
White	81%	73%
Black	10%	15%
Hispanic	7%	8%
Median Baseline Plasma HIV-1 RNA ($\log_{10}$ copies/mL) (range, $\log_{10}$ copies/mL)	4.52 (3.0-6.4)	4.56 (2.2-6.1)
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	24.4%	29.0%
Percentage of Patients with Baseline CD4+ Cell Count < 200 cells/mm^3	67%	58%
Median Darunavir FC	4.3	3.3

Table 7 compares the baseline characteristics between subjects in the PREZISTA/rtv 600/100 mg b.i.d. arm and subjects in the comparator PI arm.

Table 7: Baseline Characteristics of Subjects in the Studies TMC114-C213 and TMC114-C202 (Pooled Analysis)

	Randomized Studies TMC114-C213 and TMC114-C202	
	PREZISTA/rtv 600/100 mg b.i.d. + OBR N = 131	Comparator PI(s) + OBR N = 124
Baseline Characteristics		
Median Number of Resistance-Associated:		
PI mutations^	8	8
NNRTI mutations	1	1
NRTI mutations	6	5
Percentage of Subjects with the following Baseline IAS Primary Protease Mutations†:		
≤ 1	8%	13%
2	37%	25%
≥ 3	54%	62%
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	64%	61%
Percentage of Subjects with Prior Use of Enfuvirtide	19%	16%

^ L10F/I/R/V, K20I/L/M/R/T, L24I, D30N, V32I, L33F/I, M36I/L/V, M46I/L, I47A/V, G48V, I50L/V, F53L, I54A/L/M/S/T/V, A71V/T, G73A/C/S/T, V77I, V82A/F/L/S/T, I84A/C/V, N88D/S, L90M

† Based on the IAS-USA list of mutations (March 2005): D30N, L33F/I, M46I/L, G48V, I50L/V, V82A/F/L/S/T, I84A/C/V, L90M

‡ Only counting ARVs, excluding low-dose ritonavir, taken for at least 2 months, and for which start and stop dates were available

§ Based on phenotype (Antivirogram™)

¶ Commercially available PIs at the time of study enrollment

Week 24 outcomes for subjects on the recommended dose PREZISTA/rtv 600/100 mg b.i.d. from the pooled Studies TMC114-C213 and TMC114-C202 are shown in Table 8.

Table 8: Outcomes of Randomized Treatment Through Week 24 of the Studies TMC114-C213 and TMC114-C202 (Pooled Analysis)

	Randomized Studies TMC114-C213 and TMC114-C202	
	PREZISTA/rtv 600 mg b.i.d. + OBR N=131	Comparator PI + OBR N=124
Virologic Responders confirmed at least 1 $\log_{10}$ HIV-1 RNA below baseline through Week 24 (< 50 copies/mL at Week 24)	69.5% (45.0%)	21.0% (12.1%)
Virologic failures	26.0%	71.0%
Lack of initial response^	9.9%	57.3%
Rebound†	9.2%	9.7%
Never Suppressed‡	6.9%	4.0%
Death or discontinuation due to adverse events	3.9%	1.6%
Discontinuation due to other reasons	0.8%	6.5%

^ 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 24

‡Subjects who never reached a confirmed 1 $\log_{10}$ drop in viral load before Week 24

Through 24 weeks of treatment, the proportion of subjects with HIV-1 RNA < 400 copies/mL in the arm receiving PREZISTA/rtv 600/100 mg b.i.d. compared to the comparator PI arm was 63% and 19%, respectively. In addition, the mean changes in plasma HIV-1 RNA from baseline were -1.89 $\log_{10}$ copies/mL in the arm receiving PREZISTA/rtv 600/100 mg b.i.d. and -0.48 $\log_{10}$ copies/mL for the comparator PI arm. The mean increase from baseline in CD4+ cell counts was higher in the arm receiving PREZISTA/rtv 600/100 mg b.i.d. (92 cells/mm^3) than in the comparator PI arm (17 cells/mm^3).

The TMC114-C215/C208 analysis: Additional data on the efficacy of PREZISTA/rtv 600/100 mg b.i.d. have been obtained in treatment-experienced subjects participating in the non-randomized trials TMC114-C215 and TMC114-C208. The 246 subjects from these trials included in the TMC114-C215/C208 24-week efficacy analysis initiated therapy with PREZISTA/rtv with the recommended dose of 600/100 mg b.i.d. The OBR consisted of at least two NRTIs with or without enfuvirtide. Entry criteria for the TMC114-C215/C208 analysis were the same as those for Studies TMC114-C213 and TMC114-C202.

Baseline characteristics of the subjects included in the TMC114-C215/C208 analysis were comparable to those subjects in Studies TMC114-C213 and TMC114-C202.

The TMC114-C215/C208 24-week efficacy analysis supported the viral load reduction and CD4+ cell count increases observed in the Studies TMC114-C213 and TMC114-C202. Of the 246 subjects at Week 24, 65% had a virologic response defined as a decrease of at least 1.0 $\log_{10}$ in plasma viral load versus baseline and 40% of the subjects reached less than 50 HIV-1 RNA copies/mL. The mean increase in CD4+ cell count versus baseline was 80 cells/mm^3 at Week 20. At Week 24, 57% of the subjects reached less than 400 HIV-1 RNA copies/mL, and the mean changes in plasma HIV-1 RNA from baseline were -1.65 $\log_{10}$ copies/mL.

CONTRAINDICATIONS

PREZISTA is contraindicated in patients with known hypersensitivity to any of the ingredients of the product.

Co-administration of PREZISTA/rtv 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 (narrow therapeutic index). These drugs are listed in Table 9 (also see PRECAUTIONS, *Drug Interactions*, Table 10).

Table 9: Drugs That Are Contraindicated With PREZISTA/rtv

Drug Class	Drugs Within Class That Are Contraindicated With PREZISTA/rtv
Antihistamines	Astemizole, Terfenadine
Ergot Derivatives	Dihydroergotamine, Ergonovine, Ergotamine, Methylergonovine
GI Motility Agent	Cisapride
Neuroleptic	Pimozide
Sedative/hypnotics	Midazolam, Triazolam

Due to the need for co-administration of PREZISTA with 100 mg of ritonavir, please refer to ritonavir prescribing information for a description of ritonavir contraïndications.

WARNINGS

ALERT: Find out about medicines that should not be taken with PREZISTA/rtv. This statement is included on the product's bottle label.

General

PREZISTA (darunavir) must be co-administered with ritonavir and food to exert its therapeutic effect (see DOSAGE and ADMINISTRATION). Failure to correctly administer PREZISTA with ritonavir and food will result in reduced plasma concentrations of darunavir that will be insufficient to achieve the desired antiviral effect.

Please refer to ritonavir prescribing information for additional information on precautionary measures.

Skin Rash
During the clinical development program, severe skin rash, including erythema multiforme and Stevens-Johnson Syndrome, has been reported. 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; the discontinuation rate due to rash was 0.3%. Rashes were generally mild-to-moderate, self-limited maculopapular skin eruptions. Treatment with PREZISTA should be discontinued if severe rash develops.

Sulfa Allergy
Darunavir contains a sulfonamide moiety. PREZISTA (darunavir) should be used with caution in patients with a known sulfonamide allergy.

Drug Interactions
PREZISTA and ritonavir are both inhibitors of CYP3A. Co-administration of PREZISTA/rtv with drugs primarily metabolized by CYP3A may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse events (see sections CONTRAINDICATIONS and PRECAUTIONS, *Drug Interactions*).

Diabetes Mellitus / Hyperglycemia
New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and causal relationships between protease inhibitor therapy and these events have not been established.

PRECAUTIONS

Patients with co-existing conditions
Hepatic Impairment: Darunavir is primarily metabolized by the liver, hence, caution should be exercised when PREZISTA/rtv is given to patients with hepatic impairment, because increased plasma concentrations are expected in patients with hepatic impairment. There are no data regarding the use of PREZISTA/rtv when co-administered to patients with varying degrees of hepatic impairment; therefore, specific dosage recommendations cannot be made. PREZISTA/rtv should be used with caution in patients with hepatic impairment (see CLINICAL PHARMACOLOGY, *Pharmacokinetics in Adults*, *Special Populations*, *Hepatic Impairment* and DOSAGE AND ADMINISTRATION).

Patients with pre-existing liver dysfunction, including chronic active hepatitis, can have an increased frequency of liver function abnormalities during combination antiretroviral therapy and should be monitored according to standard practice. If there is evidence of worsening of liver disease in such patients, interruption or discontinuation of treatment must be considered.

Renal Impairment: Population pharmacokinetic analysis showed that the pharmacokinetics of darunavir were not significantly affected in HIV infected subjects with moderate renal impairment (CrCL between 30-60 mL/min, n=20). There are no pharmacokinetic data available in HIV-1 infected patients with severe renal impairment or end stage renal disease; however,

since the renal clearance of darunavir is limited, a decrease in total body clearance is not expected in patients with renal impairment. As darunavir and ritonavir are highly bound to plasma proteins, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis (see CLINICAL PHARMACOLOGY, *Pharmacokinetics in Adults*, *Special Populations*, *Renal Impairment* and DOSAGE AND ADMINISTRATION).

Hemophilia: There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis in patients with hemophilia type A and B treated with protease inhibitors. In some patients, additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship between protease inhibitor therapy and these episodes has not been established.

Fat Redistribution
Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Immune Reconstitution Syndrome
During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* complex, cytomegalovirus, *Pneumocystis jeroveci* pneumonia, and tuberculosis), which may necessitate further evaluation and treatment.

Resistance/Cross-Resistance
Because the potential for HIV cross-resistance among protease inhibitors has not been fully explored in PREZISTA/rtv treated patients, it is unknown what effect therapy with PREZISTA will have on the activity of subsequently administered protease inhibitors.

Information for Patients
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.

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. The long-term effects of PREZISTA are unknown at this time. 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.

Patients should be advised to take PREZISTA and ritonavir (NORVIR®) with food every day as prescribed. The type of food does not affect exposure to PREZISTA. Patients should be instructed to swallow whole tablets with a drink such as water or milk. PREZISTA must always

be used with 100 mg of 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. 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®) at any one time.

PREZISTA/rtv 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/rtv because hormonal levels may decrease.

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

Drug Interactions

PREZISTA and ritonavir are both inhibitors of CYP3A. Co-administration of PREZISTA and ritonavir with drugs that are primarily metabolized by CYP3A may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse events (see Tables 10 and 11).

Drugs that are contraindicated and not recommended for co-administration with PREZISTA/rtv are included in Table 10. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

Table 10: Drugs That Should Not Be Co-administered With PREZISTA/rtv

Drug Class: Drug Name	Clinical Comment
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	Carbamazepine, phenobarbital and phenytoin are inducers of CYP450 enzymes. PREZISTA/rtv should not be used in combination with phenobarbital, phenytoin, or carbamazepine as co-administration may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to PREZISTA.
Antihistamines: astemizole, terfenadine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimycobacterial: rifampin	Rifampin is a potent inducer of CYP450 metabolism. PREZISTA/rtv should not be used in combination with rifampin, as this may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to PREZISTA.
Ergot Derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Gastrointestinal Motility Agent: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products: St. John's wort (*Hypericum perforatum*)	PREZISTA/rtv should not be used concomitantly with products containing St. John's wort (*Hypericum perforatum)* because co-administration may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to PREZISTA.
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis. For dosing recommendation regarding atorvastatin and pravastatin, see Table 11: Established and Other