

NDA 21-976/S003
NDA 21-976/S004

- 4 -

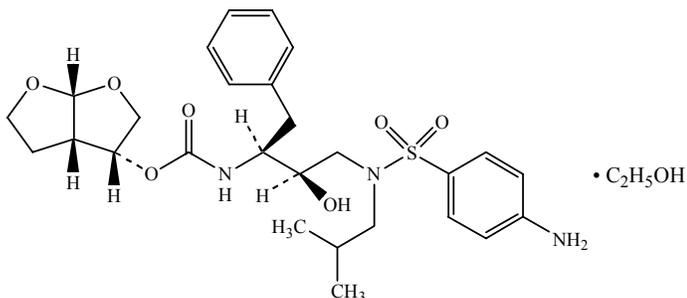
PREZISTA™* (Tibotec, Inc.) (darunavir)

Tablets

1. DESCRIPTION

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

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



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

PREZISTA 300 mg and PREZISTA 600 mg tablets are available as orange, oval-shaped, film-coated tablets for oral administration. Each 300 mg tablet contains darunavir ethanolate equivalent to 300 mg of darunavir. Each 600 mg tablet contains darunavir ethanolate equivalent to 600 mg of darunavir. During storage, partial conversion from ethanolate to hydrate may occur; however, this does not affect product quality or performance. Each tablet also contains the inactive ingredients colloidal silicon dioxide, crospovidone, magnesium stearate, and microcrystalline cellulose. The tablet film coating, OPADRY® Orange, contains FD&C Yellow No. 6, polyethylene glycol 3350, polyvinyl alcohol-partially hydrolyzed, talc, and titanium dioxide.

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

NDA 21-976/S003
NDA 21-976/S004

- 5 -

2. 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 EC₅₀ 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 EC₅₀ values ranging from < 0.1 to 4.3 nM. The EC₅₀ value of darunavir increases by a median factor of 5.4 in the presence of human serum. Darunavir did not show antagonism when studied in combination with the protease inhibitors amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, or tipranavir, the N(t)RTIs abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, zalcitabine, or zidovudine, the NNRTIs delavirdine, efavirenz, or nevirapine, and the fusion inhibitor enfuvirtide.

Resistance

Cell Culture: HIV-1 isolates with a decreased susceptibility to darunavir have been selected in cell culture and obtained from subjects treated with darunavir/ritonavir. Darunavir-resistant virus derived in cell culture from wild-type HIV had 6- to 21-fold decreased susceptibility to darunavir and harbored 3 to 6 of the following amino acid substitutions S37N/D, R41E/S/T, K55Q, K70E, A71T, T74S, V77I, or I85V in the protease. Selection in cell culture of darunavir resistant HIV-1 from nine HIV-1 strains harboring multiple protease inhibitor resistance-associated mutations resulted in the overall emergence of 22 mutations in the protease gene, including L10F, V11I, I13V, I15V, G16E, L23I, V32I, L33F, S37N, M46I, I47V, I50V, F53L, L63P, A71V, G73S, L76V, V82I, I84V, T91A/S, and Q92R, of which L10F, V32I, L33F, S37N, M46I, I47V, I50V, L63P, A71V, and I84V were the most prevalent. These darunavir-resistant viruses had at least eight protease mutations and exhibited 50- to 641-fold decreases in darunavir susceptibility with final EC₅₀ values ranging from 125 nM to 3461 nM.

NDA 21-976/S003
NDA 21-976/S004

- 6 -

Clinical studies of darunavir/ritonavir in treatment-experienced subjects

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

Cross-resistance

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

NDA 21-976/S003
NDA 21-976/S004

- 7 -

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.

PI Mutations [^]	Prezista/rtv 600/100 mg (n = 125)				Comparative Arm (n = 120)			
	n	Proportion of subjects with $\geq 1 \log_{10}$ decrease at Week 24	Proportion of subjects with < 50 copies/mL at Week 24	Median DAVG ₂₄	n	Proportion of subjects with $\geq 1 \log_{10}$ 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

NDA 21-976/S003

- 8 -

NDA 21-976/S004

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.

Baseline Darunavir Phenotype N = 340 (fold change ranges)	Proportion of subjects with ≥1 log₁₀ 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

3. 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.

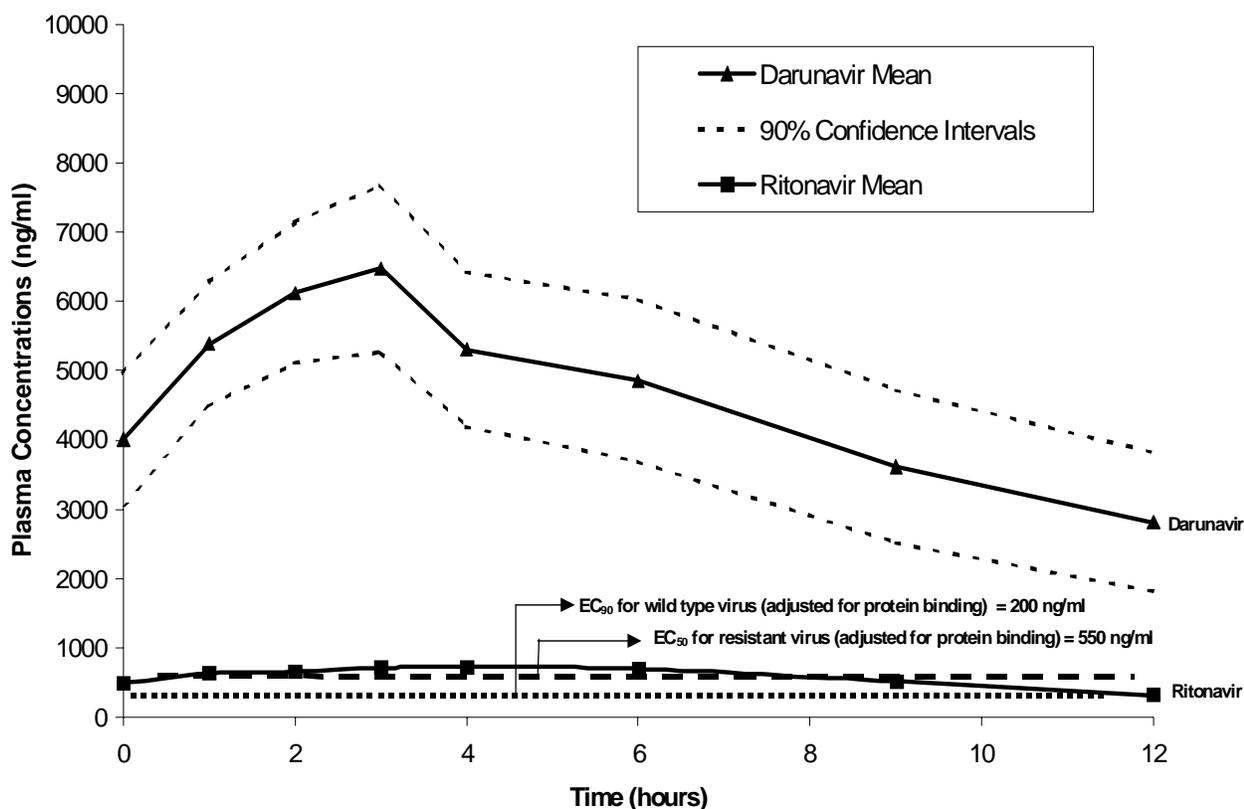
NDA 21-976/S003
 NDA 21-976/S004

- 9 -

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)



NDA 21-976/S003
NDA 21-976/S004

- 10 -

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. *In vivo* data suggests that darunavir/ritonavir is an inhibitor of the p-glycoprotein (p-gp) transporters.

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.

NDA 21-976/S003
NDA 21-976/S004

- 11 -

Special Populations

Hepatic Impairment: Darunavir is primarily metabolized by the liver. The steady-state pharmacokinetic parameters of darunavir were similar after multiple dose co-administration of PREZISTA/rtv 600/100 mg b.i.d. to subjects with normal hepatic function (n=16), mild hepatic impairment (Child-Pugh Class A, n=8), and moderate hepatic impairment (Child-Pugh Class B, n=8). The effect of severe hepatic impairment on the pharmacokinetics of darunavir has not been evaluated (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 ¹⁴C-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 ≥ 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.

NDA 21-976/S003
NDA 21-976/S004

- 12 -

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*.

NDA 21-976/S003

- 13 -

NDA 21-976/S004

Table 4: Drug Interactions: Pharmacokinetic Parameters for <u>Darunavir</u> in the Presence of Co-administered Drugs							
Co-Administered Drug	Dose/Schedule		N	PK	LS Mean Ratio (90% CI) of <u>Darunavir</u> 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.	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)
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)

NDA 21-976/S003
NDA 21-976/S004

- 14 -

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)
<p>N = number of subjects with data; - = no information available. [^] q.d. = 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.</p>							

NDA 21-976/S003
NDA 21-976/S004

- 15 -

Table 5: Drug Interactions: Pharmacokinetic Parameters for <u>Co-administered Drugs</u> in the Presence of Darunavir/Ritonavir							
Co-Administered Drug	Dose/Schedule		N	PK	LS Mean Ratio (90% CI) of <u>Co-Administered Drug</u> Pharmacokinetic Parameters With/Without Darunavir 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.^ /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. ‡ 533/133.3 mg b.i.d. ‡	1200/100 mg b.i.d. 1200 mg b.i.d.	14 15	↔ ↔	0.98 (0.78- 1.22)	1.09 (0.86- 1.37)	1.23 (0.90- 1.69) 1.13 (0.90- 1.42)
Saquinavir hard gel capsule	1000 mg b.i.d. /100 mg RTV 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)

NDA 21-976/S003
NDA 21-976/S004

- 16 -

	administered alone						
	1000 mg b.i.d. when administered with darunavir/ritonavir						
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)
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)

NDA 21-976/S003
NDA 21-976/S004

- 17 -

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)
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)
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	400/100 mg b.i.d.	16	↑	0.62 (0.55- 0.70)	0.97 (0.86- 1.09)	-

NDA 21-976/S003

- 18 -

NDA 21-976/S004

	dose) when administered with darunavir/ ritonavir						
<p>N = number of subjects with data; - = no information available. [^] q.d. = 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.</p>							

4. 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.

NDA 21-976/S003
NDA 21-976/S004

- 19 -

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 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 1.0 log₁₀ 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.

NDA 21-976/S003
NDA 21-976/S004

- 20 -

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

NDA 21-976/S003

- 21 -

NDA 21-976/S004

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		

NDA 21-976/S003
NDA 21-976/S004

- 22 -

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 log₁₀ copies/mL in the arm receiving PREZISTA/rtv 600/100 mg b.i.d. and -0.48 log₁₀ 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/mm³) than in the comparator PI arm (17 cells/mm³).

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.

NDA 21-976/S003

- 23 -

NDA 21-976/S004

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 log₁₀ 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/mm³ 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 log₁₀ copies/mL.

5. 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).

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 contraindications.

NDA 21-976/S003
NDA 21-976/S004

- 24 -

6. 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.

Hepatotoxicity

Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported with PREZISTA/rtv. During the clinical development program (N=3063), hepatitis has been reported in 0.5% of patients receiving combination therapy with PREZISTA/rtv. Patients with pre-existing liver dysfunction, including chronic active hepatitis B or C, have an increased risk for liver function abnormalities including severe hepatic adverse events.

Post-marketing cases of liver injury, including some fatalities, have been reported. These have generally occurred in patients with advanced HIV-1 disease taking multiple concomitant medications, having co-morbidities including hepatitis B or C co-infection, and/or developing immune reconstitution syndrome. A causal relationship with PREZISTA/rtv therapy has not been established.

Appropriate laboratory testing should be conducted prior to initiating therapy with PREZISTA/rtv and patients should be monitored during treatment. Increased AST/ALT monitoring should be considered in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases, especially during the first several months of PREZISTA/rtv treatment.

If there is evidence of new or worsening liver dysfunction (including clinically significant elevation of liver enzymes and/or symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, hepatomegaly) in patients on PREZISTA/rtv, interruption or discontinuation of treatment must be considered.

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.

NDA 21-976/S003

- 25 -

NDA 21-976/S004

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.

NDA 21-976/S003
NDA 21-976/S004

- 26 -

7. PRECAUTIONS

Patients with co-existing conditions

Hepatic Impairment: No dose adjustment of PREZISTA/rtv is necessary for patients with either mild or moderate hepatic impairment. There are no pharmacokinetic or safety data available for subjects with severe hepatic impairment, therefore, PREZISTA/rtv is not recommended for use in patients with severe hepatic impairment (see CLINICAL PHARMACOLOGY, *Pharmacokinetics in Adults, Special Populations, Hepatic Impairment* and DOSAGE AND ADMINISTRATION).

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 jirovecii* 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.

NDA 21-976/S003

- 27 -

NDA 21-976/S004

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

NDA 21-976/S003

- 28 -

NDA 21-976/S004

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.

NDA 21-976/S003
NDA 21-976/S004

- 29 -

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 (<i>Hypericum perforatum</i>)	PREZISTA/rtv should not be used concomitantly with products containing St. John's wort (<i>Hypericum perforatum</i>) 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

NDA 21-976/S003
NDA 21-976/S004

- 30 -

	Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction.
Neuroleptic: pimozide	CONTRAINDICATED due to the potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Sedative/Hypnotics: midazolam, triazolam	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

**Table 11: Established and Other Potentially Significant Drug Interactions:
Alterations in Dose or Regimen May Be Recommended
Based on Drug Interaction Studies or Predicted Interaction
(See CLINICAL PHARMACOLOGY for Magnitude of Interaction, Tables 4 and 5)**

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Efavirenz	↓ darunavir ↑ efavirenz	Co-administration of darunavir/rtv and efavirenz decreased darunavir AUC by 13% and C _{min} by 31%. The AUC of efavirenz increased by 21% and C _{min} increased by 17%. The clinical significance has not been established. The combination of PREZISTA/rtv and efavirenz should be used with caution.
Nevirapine	↔ darunavir ↑ nevirapine	PREZISTA/rtv and nevirapine can be co-administered without any dose adjustments.
HIV-Antiviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		

NDA 21-976/S003
NDA 21-976/S004

- 31 -

Didanosine	↔ darunavir ↔ didanosine	PREZISTA/rtv (600/100 mg b.i.d.) did not significantly affect didanosine exposure. The combination of PREZISTA co-administered with 100 mg ritonavir and didanosine can be used without dose adjustments. It is recommended that didanosine be administered on an empty stomach. Therefore, didanosine should be administered one hour before or two hours after PREZISTA/rtv (which are administered with food).
Tenofovir Disoproxil Fumarate	↔ darunavir ↑ tenofovir	PREZISTA/rtv and tenofovir disoproxil fumarate can be co-administered without any dose adjustments.
HIV-Antiviral Agents: HIV-Protease Inhibitors (PIs)		
Atazanavir (The reference regimen for atazanavir was atazanavir/ritonavir 300/100 mg q.d.)	↔ darunavir ↔ atazanavir	PREZISTA/rtv and atazanavir (300 mg q.d.) can be co-administered.
Indinavir (The reference regimen for indinavir was indinavir/ritonavir 800/100 mg b.i.d.)	↑ darunavir ↑ indinavir	The appropriate dose of indinavir in combination with PREZISTA/rtv has not been established.
Lopinavir/ritonavir	↓ darunavir ↔ lopinavir	Due to decrease in the exposure (AUC) of darunavir, appropriate doses of the combination have not been established. Hence, it is not recommended to co-administer lopinavir/ritonavir and PREZISTA, with or without an additional low-

NDA 21-976/S003
NDA 21-976/S004

- 32 -

		dose of ritonavir.
Saquinavir	↓ darunavir ↔ saquinavir	Due to a decrease in the exposure (AUC) of darunavir by 26%, appropriate doses of the combination have not been established. Hence, it is not recommended to co-administer saquinavir and PREZISTA, with or without low-dose ritonavir.
Other Agents		
Antiarrhythmics: bepridil, lidocaine (systemic), quinidine, amiodarone	↑ antiarrhythmics	Concentrations of bepridil, lidocaine, quinidine and amiodarone may be increased when co-administered with PREZISTA/rtv. Caution is warranted and therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when co-administered with PREZISTA/rtv.
digoxin	↑ digoxin	Concomitant use of PREZISTA/rtv with digoxin results in a significant increase in serum concentrations of digoxin. It is recommended that the lowest dose of digoxin should initially be prescribed. The serum digoxin concentrations should be monitored and used for titration of digoxin dose to obtain the desired clinical effect.
Anticoagulant: warfarin	↓ warfarin ↔ darunavir	Warfarin concentrations may be affected when co-administered with PREZISTA/rtv. It is recommended that the international normalized ratio (INR) be monitored when warfarin is combined with

NDA 21-976/S003
NDA 21-976/S004

- 33 -

		PREZISTA/rtv.
Antidepressant: trazodone	↑ trazodone	Concomitant use of trazodone and PREZISTA/rtv may increase plasma concentrations of trazodone. Adverse events of nausea, dizziness, hypotension and syncope have been observed following co-administration of trazodone and ritonavir. If trazodone is used with a CYP3A inhibitor such as PREZISTA/rtv, the combination should be used with caution and a lower dose of trazodone should be considered.
Anti-infective: clarithromycin	↑ clarithromycin	No dose adjustment of darunavir or clarithromycin is required for patients with normal renal function. For patients with renal impairment, the following dose adjustments should be considered: <ul style="list-style-type: none"> • For subjects with CLcr of 30-60 mL/min, the dose of clarithromycin should be reduced by 50%. • For subjects with CLcr of < 30 mL/min, the dose of clarithromycin should be reduced by 75%.
Antifungals: ketoconazole, itraconazole, voriconazole	↑ ketoconazole ↑ darunavir ↑ itraconazole (not studied) ↓ voriconazole	Ketoconazole and itraconazole are potent inhibitors as well as substrates of CYP3A. Concomitant systemic use of

NDA 21-976/S003
NDA 21-976/S004

- 34 -

	(not studied)	<p>ketoconazole, itraconazole, and darunavir/ritonavir may increase plasma concentration of darunavir.</p> <p>Plasma concentrations of ketoconazole or itraconazole may be increased in the presence of darunavir/ritonavir. When co-administration is required, the daily dose of ketoconazole or itraconazole should not exceed 200 mg.</p> <p>Co-administration of voriconazole with darunavir/ritonavir has not been studied. Administration of voriconazole with ritonavir (100 mg twice daily) decreased the AUC of voriconazole by an average of 39%. Voriconazole should not be administered to patients receiving darunavir/ritonavir unless an assessment of the benefit/risk ratio justifies the use of voriconazole.</p>
<p>Antimycobacterial: rifabutin</p>	<p>↑ rifabutin ↓ darunavir</p>	<p>Rifabutin is an inducer and substrate of CYP450 enzymes. Concomitant use of rifabutin and darunavir in the presence of ritonavir is expected to increase rifabutin plasma concentrations and decrease darunavir plasma concentrations. When indicated, it is recommended to administer rifabutin at a dosage of 150 mg once every other day when co-administered with PREZISTA/rtv.</p>

NDA 21-976/S003
NDA 21-976/S004

- 35 -

<p>Calcium Channel Blockers: felodipine, nifedipine, nicardipine</p>	<p>↑ calcium channel blockers</p>	<p>Plasma concentrations of calcium channel blockers (e.g. felodipine, nifedipine, nicardipine) may increase when PREZISTA/rtv are co-administered. Caution is warranted and clinical monitoring of patients is recommended.</p>
<p>Corticosteroid: dexamethasone fluticasone propionate</p>	<p>↓ darunavir ↑ fluticasone propionate</p>	<p>Use with caution. Systemic dexamethasone induces CYP3A and can thereby decrease darunavir plasma concentrations. This may result in loss of therapeutic effect to PREZISTA. Concomitant use of inhaled fluticasone propionate and PREZISTA/rtv may increase plasma concentrations of fluticasone propionate. Alternatives should be considered, particularly for long term use.</p>
<p>HMG-CoA Reductase Inhibitors: pravastatin, atorvastatin, rosuvastatin</p>	<p>↑ pravastatin ↑ atorvastatin ↑ rosuvastatin</p>	<p>When PREZISTA/rtv was administered with pravastatin, the mean increase in pravastatin AUC was 81%. However, pravastatin AUC increased by up to 5-fold in some subjects. The mechanism of the interaction is not known.</p> <p>Use the lowest possible dose of atorvastatin, pravastatin or rosuvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as fluvastatin in combination with PREZISTA/rtv.</p>

NDA 21-976/S003
NDA 21-976/S004

- 36 -

H2-Receptor Antagonists and Proton Pump Inhibitors: omeprazole, ranitidine	↔ darunavir	PREZISTA/rtv can be co-administered with H2-receptor antagonists and proton pump inhibitors without any dose adjustments.
Immunosuppressants: cyclosporine, tacrolimus, sirolimus	↑ immunosuppressants	Plasma concentrations of cyclosporine, tacrolimus or sirolimus may be increased when co-administered with PREZISTA/rtv. Therapeutic concentration monitoring of the immunosuppressive agent is recommended for immunosuppressant agents when co-administered with PREZISTA/rtv.
Narcotic Analgesic: methadone	↓ methadone	No adjustment of methadone dosage is required when initiating coadministration of PREZISTA/rtv. However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.
Oral Contraceptives/estrogen: ethinyl estradiol norethindrone	↓ ethinyl estradiol ↓ norethindrone	Plasma concentrations of ethinyl estradiol are decreased due to induction of its metabolism by ritonavir. Alternative methods of nonhormonal contraception are recommended.
PDE-5 inhibitors: sildenafil, vardenafil, tadalafil	↑ PDE-5 inhibitors	Concomitant use of PDE-5 inhibitors with PREZISTA/rtv should be done with caution. If concomitant use of PREZISTA/rtv with

NDA 21-976/S003
NDA 21-976/S004

- 37 -

		sildenafil, vardenafil, or tadalafil is required, sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg dose in 72 hours, or tadalafil at a single dose not exceeding 10 mg dose in 72 hours, is recommended.
Selective Serotonin Reuptake Inhibitors (SSRIs): sertraline, paroxetine	↔ darunavir ↓ sertraline ↓ paroxetine	If sertraline or paroxetine is co-administered with PREZISTA/rtv, the recommended approach is a careful dose titration of the SSRI based on a clinical assessment of antidepressant response. In addition, patients on a stable dose of sertraline or paroxetine who start treatment with PREZISTA/rtv should be monitored for antidepressant response.

Other NRTIs:

Based on the different elimination pathways of the other NRTIs (zidovudine, zalcitabine, emtricitabine, stavudine, lamivudine and abacavir) that are primarily renally excreted, no drug interactions are expected for these drugs and PREZISTA/rtv.

Other protease inhibitors:

The co-administration of PREZISTA/rtv and PIs other than lopinavir/ritonavir, saquinavir, atazanavir, and indinavir has not been studied. Therefore, such co-administration is not recommended.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis:

Long-term carcinogenicity studies of darunavir in rodents have not been completed. Darunavir, however, was tested negative in the *in vitro* Ames reverse mutation assay and *in vitro* chromosomal aberration assay in human lymphocytes, both tested in the absence and presence of metabolic activation system. Darunavir does not induce chromosomal damage in the *in vivo* micronucleus test in mice.

Impairment of Fertility:

NDA 21-976/S003

- 38 -

NDA 21-976/S004

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

NDA 21-976/S003
NDA 21-976/S004

- 39 -

Pregnancy

Pregnancy Category B: Reproduction studies conducted with darunavir have shown no embryotoxicity or teratogenicity in mice, rats and rabbits. Because of limited bioavailability of darunavir in animals and/or dosing limitations, the plasma exposures (AUC values) were approximately 50% in mice and rats and 5% in the rabbit of those obtained in humans at the recommended clinical dose boosted with ritonavir.

In the rat pre- and postnatal development study, a reduction in pup body weight gain was observed with darunavir alone or in combination with ritonavir during lactation. This was due to exposure of pups to drug substances via the milk. Sexual development, fertility or mating performance of offspring was not affected by maternal treatment with darunavir alone or in combination with ritonavir. The maximal plasma exposures achieved in rats were approximately 50% of those obtained in humans at the recommended clinical dose boosted with ritonavir.

There are, however, no adequate and well-controlled studies in pregnant women. PREZISTA should be used during pregnancy only if the potential benefit justifies the potential risk.

Antiretroviral Pregnancy Registry: *To monitor maternal-fetal outcomes of pregnant women exposed to PREZISTA, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.*

Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Although it is not known whether darunavir is secreted in human milk, darunavir is secreted into the milk of lactating rats. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breastfeed if they are receiving PREZISTA.**

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of PREZISTA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, caution should be exercised in the administration and monitoring of PREZISTA in elderly patients reflecting the greater frequency of decreased hepatic function, and of concomitant disease or other drug therapy.

NDA 21-976/S003
NDA 21-976/S004

- 40 -

8. ADVERSE REACTIONS

The safety assessment is based on all safety data from the Studies TMC114-C213 and TMC114-C202 and the TMC114-C215/C208 analysis reported with the recommended dose PREZISTA/rtv 600/100 mg b.i.d. in the 458 subjects who initiated treatment with the recommended dose (*de novo* subjects). In Studies TMC114-C213 and TMC114-C202, the mean exposure in weeks for subjects in the PREZISTA/rtv 600/100 mg b.i.d. arm and comparator PI arm was 63.5 and 31.5, respectively. The mean exposure in weeks for subjects in the TMC114-C215/C208 analysis was 23.9.

The most common treatment-emergent adverse events (> 10%) reported in the *de novo* subjects, regardless of causality or frequency, were diarrhea, nausea, headache, and nasopharyngitis.

For subjects in the PREZISTA/rtv 600/100 mg b.i.d. arm and the comparator PI arm in the pooled analysis for Studies TMC114-C213 and TMC114-C202, diarrhea was reported in 19.8% and 28.2%, nausea in 18.3% and 12.9%, headache in 15.3% and 20.2%, and nasopharyngitis in 13.7% and 10.5%, of subjects, respectively. In the randomized trials, rates of discontinuation of therapy due to adverse events were 9% in subjects receiving PREZISTA/rtv and in 5% of subjects in the comparator PI arm.

Due to the need for co-administration of PREZISTA with 100 mg of ritonavir, please refer to ritonavir prescribing information for ritonavir-associated adverse reactions.

Drug-related clinical adverse events of moderate or severe intensity (\geq Grade 2) occurring in \geq 2% of subjects treated with PREZISTA/rtv for 1 to 96 weeks are presented in Table 12.

Table 12: Percentage of Subjects with Selected Treatment Emergent, Drug-Related[^] Adverse Events of at least Moderate Intensity (Grades 2-4) in \geq 2% of Adult Subjects in Any PREZISTA/rtv Treatment Groups[†]			
System Organ Class, Preferred Term, %	Randomized Studies TMC114-C213 and TMC114-C202		Non-randomized TMC114-C215/C208 Analysis
	PREZISTA/rtv 600/100 mg b.i.d. +OBR N = 131	Comparator PI +OBR N = 124	PREZISTA/rtv 600/100 mg b.i.d. +OBR N = 327
Gastrointestinal Disorders			
Diarrhea	2.3%	3.2%	2.8%
Vomiting	1.5%	1.6%	2.4%
Abdominal Pain	2.3%	0.8%	1.2%
Constipation	2.3%	0.8%	0.6%
Nervous System Disorders			
Headache	3.8%	2.4%	0.9%

NDA 21-976/S003

- 41 -

NDA 21-976/S004

[^] Includes adverse events at least possibly, probably, or very likely related to the drug
N=total number of subjects per treatment group
[†] Excludes laboratory abnormalities that were reported as Adverse Events (see Table 13:
Treatment Emergent Grade 2 to 4 Laboratory Abnormalities Reported in $\geq 2\%$ of Subjects)

Treatment-emergent adverse events occurring in less than 2% of *de novo* subjects (n=458) receiving PREZISTA/rtv, considered at least possibly related to treatment and of at least moderate intensity are listed below by body system:

Body as a Whole:

folliculitis, asthenia, pyrexia, fatigue, rigors, hyperthermia, peripheral edema

Cardiovascular System:

myocardial infarction, tachycardia, hypertension

Digestive System:

flatulence, abdominal distension, dry mouth, dyspepsia, abdominal pain, nausea, constipation

Metabolic and Nutritional Disorders:

anorexia, hypercholesterolemia, hyperlipidemia, diabetes mellitus, decreased appetite, obesity, fat redistribution, hyponatremia, polydipsia

Musculoskeletal System:

arthralgia, pain in extremity, myalgia, osteopenia, osteoporosis

Nervous System:

peripheral neuropathy, hypoesthesia, memory impairment, paresthesia, somnolence, transient ischemic attack, confusional state, disorientation, irritability, altered mood, nightmare, anxiety, headache

Respiratory System:

dyspnea, cough, hiccups

Skin and Appendages:

lipatrophy, night sweats, allergic dermatitis, eczema, toxic skin eruption, alopecia, dermatitis medicamentosa, hyperhidrosis, skin inflammation, maculopapular rash

Special Senses:

vertigo

Urogenital System:

acute renal failure, renal insufficiency, nephrolithiasis, polyuria, gynecomastia

NDA 21-976/S003
NDA 21-976/S004

- 42 -

Laboratory abnormalities:

The percentages of adult subjects treated with PREZISTA/rtv 600/100 mg b.i.d. with treatment-emergent Grade 2 to 4 laboratory abnormalities are presented in Table 13.

Table 13: Treatment Emergent Grade 2 to 4 Laboratory Abnormalities Reported in ≥ 2% of Subjects				
		Randomized Studies TMC114-C213 and TMC114-C202		Non- randomized TMC114- C215/C208 Analysis
Laboratory Parameter Preferred Term, %	Limit	PREZISTA/ rtv 600/100 mg b.i.d. + OBR N = 131	Comparator PI + OBR N = 124	PREZISTA/ rtv 600/100 mg b.i.d. N = 327
Biochemistry				
Aspartate Aminotransferase	> 2.5 X ULN	10.0%	13.0%	5.3%
Alanine Aminotransferase	> 2.5 X ULN	6.9%	9.8%	5.6%
Gamma Glutamyl Transferase	> 2.5 X ULN	9.2%	8.9%	8.4%
Hyperbilirubinemia	> 1.5 X ULN	2.3%	15.4%	0.9%
Alkaline Phosphatase	> 2.5 X ULN	4.6%	0%	2.8%
Pancreatic Amylase	> 1.5 X ULN	16.9%	8.9%	10.8%
Pancreatic Lipase	> 1.5 X ULN	8.5%	4.1%	6.2%
Hyperglycemia	≥ 161 mg/dL	2.3%	8.1%	5.9%
Hypoglycemia	≤ 54 mg/dL	1.5%	1.6%	3.7%
Total Cholesterol	≥ 240 mg/dL	9.2%	3.3%	8.0%
Triglycerides	> 400 mg/dL	25.4%	26.0%	18.9%
Hypoalbuminemia	< 3 g/dL	3.1%	1.6%	4.3%
Hyperuricemia	≥ 9.9 mg/dL	6.9%	6.5%	2.2%
Bicarbonate	< 15 mmol/L	3.1%	4.1%	3.4%
Hypocalcemia	≤ 7.8 mg/dL	0%	0.8%	4.0%
Hyponatremia	≤ 129 meq/L	0.8%	0%	2.5%
Hypernatremia	≥ 151 meq/L	2.3%	0%	0%
Hematology				
White Blood Cell Count decrease	< 3000 count/mm ³	15.4%	18.7%	13.0%
Total Absolute Neutrophil Count	≤ 999 mm ³	6.9%	9.8%	11.5%

NDA 21-976/S003

- 43 -

NDA 21-976/S004

decrease				
Lymphocytes decrease	< 1000 count/mm ³	4.6%	19.5%	10.9%
Partial Thromboplastin Time increase	> 1.66 X ULN	7.8%	4.1%	4.3%
Plasma Prothrombin Time increase	> 1.25 X ULN	3.9%	0.8%	0.6%
Platelet Count decrease	< 75,000/mm ³	3.1%	1.6%	2.8%

Additional adverse reactions identified in clinical studies, occurring in less than 1% of the patients, are listed below by body system:

Hepatobiliary System: acute hepatitis, cytolytic hepatitis, hepatotoxicity, hyperbilirubinemia

Skin and Appendages: erythema multiforme, Stevens-Johnson Syndrome

Patients co-infected with hepatitis B and/or hepatitis C virus:

In subjects co-infected with hepatitis B or C virus receiving PREZISTA/rtv, the incidence of adverse events and clinical chemistry abnormalities was not higher than in subjects receiving PREZISTA/rtv who were not co-infected, except for increased hepatic enzymes (see WARNINGS, *Hepatotoxicity*). The pharmacokinetic exposure in co-infected subjects was comparable to that in subjects without co-infection.

9. OVERDOSAGE

Human experience of acute overdose with PREZISTA/rtv is limited. Single doses up to 3200 mg of the oral solution of darunavir alone and up to 1600 mg of the tablet formulation of darunavir in combination with ritonavir have been administered to healthy volunteers without untoward symptomatic effects.

There is no specific antidote for overdose with PREZISTA. Treatment of overdose with PREZISTA consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. If indicated, elimination of unabsorbed active substance is to be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since PREZISTA is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the active substance.

NDA 21-976/S003
NDA 21-976/S004

- 44 -

10. DOSAGE AND ADMINISTRATION

Adults: The recommended oral dose of PREZISTA tablets is 600 mg (two 300 mg tablets or one 600 mg tablet) twice daily taken with ritonavir 100 mg twice daily and with food. The type of food does not affect exposure to darunavir.

Pediatric Patients: The safety and efficacy of PREZISTA in pediatric patients has not been established (see CLINICAL PHARMACOLOGY, *Special Populations, Pediatric Patients*).

Hepatic Impairment: No dose adjustment is required in patients with mild or moderate hepatic impairment. There are no data regarding the use of PREZISTA/rtv when co-administered to subjects with severe hepatic impairment; therefore, PREZISTA/rtv is not recommended for use in patients with severe hepatic impairment (see CLINICAL PHARMACOLOGY, *Pharmacokinetics in Adults, Special Populations, Hepatic Impairment* and PRECAUTIONS, *Patients with co-existing conditions, Hepatic Impairment*).

Renal Impairment: No dose adjustment is required in patients with moderate renal impairment. There are no pharmacokinetic data available in HIV-1 infected patients with severe renal impairment or end stage renal disease (see CLINICAL PHARMACOLOGY, *Pharmacokinetics in Adults, Special Populations, Renal Impairment* and PRECAUTIONS, *Patients with co-existing conditions, Renal Impairment*).

11. HOW SUPPLIED

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) 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 “” (curved triangle with a dot) on the other side.

PREZISTA tablets are packaged in bottles in the following configuration:

- 300 mg tablets—bottles of 120 (NDC 59676-560-01)
- 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).

Rx Only

NDA 21-976/S003
NDA 21-976/S004

- 45 -



Manufactured for Tibotec, Inc. by:
JOLLC, Gurabo, Puerto Rico

Distributed by:

Tibotec Therapeutics, Division of Ortho Biotech Products, L.P., Raritan NJ 08869

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

© Tibotec, Inc. 2006

Revised: February 2008

10101704

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 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.

12. WHAT IS PREZISTA?

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

13. 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 may 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 100 mg of ritonavir (NORVIR®), in combination with other anti-HIV medicines. PREZISTA should also be taken with food.

14. 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.

*Trademark of Tibotec Pharmaceuticals, Ltd.

15. 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.

16. 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 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.

17. WHO SHOULD NOT TAKE PREZISTA?*

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

Do not take PREZISTA if you:

- are allergic to darunavir or any of the other ingredients in PREZISTA
- are allergic to ritonavir (NORVIR®)
- take any of the following types of medicines because you could experience serious side effects:

<u>Type of Drug</u>	<u>Examples of Generic Names (Brand Names)</u>
Antihistamines (to treat allergy symptoms)	astemizole (Hismanal®) terfenadine (Seldane®)
Ergot Derivatives (to treat migraine and headaches)	dihydroergotamine (D.H.E. 45®, Migranal®) ergonovine ergotamine (Wigraine®, Ergostat®, Cafergot®, Ergomar®) methylergonovine
Gastrointestinal Motility Agent (to treat some digestive conditions)	cisapride (Propulsid®)
Neuroleptic (to treat psychiatric conditions)	pimozide (Orap®)
Sedative/hypnotics (to treat trouble with sleeping and/or anxiety)	midazolam (Versed®) triazolam (Halcion®)

18. 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, including St. John's wort (*Hypericum perforatum*). 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. 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.

** The brands listed are the registered trademarks of their respective owners and are not trademarks of Tibotec, Inc.

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

<u>Type of Drug</u>	<u>Examples of Generic Names (Brand Names)</u>
Antiarrhythmics (to treat abnormal heart rhythms)	bepriidil (Vascor [®]) lidocaine (Lidoderm [®]) quinidine amiodarone (Cordarone [®]) digoxin (Lanoxin [®])
Anticoagulants (to prevent the clotting of red blood cells called platelets)	warfarin (Coumadin [®])
Anticonvulsants (to treat epilepsy and prevent seizures)	carbamazepine (Tegretol [®] , Carbatrol [®]) phenobarbital phenytoin (Dilantin [®] , Phenytek [®])
Antidepressants	trazodone (Desyrel [®])
Anti-infectives (to treat bacterial infections)	clarithromycin (Biaxin [®])
Antifungals (to treat fungal infections)	ketoconazole (Nizoral [®]) itraconazole (Sporanox [®]) voriconazole (Vfend [®])
Antimycobacterials (to treat bacterial infections)	rifabutin (Mycobutin [®]) rifampin (Rifadin [®] , Rifater [®] , Rifamate [®])
Calcium Channel Blockers (to treat heart disease)	felodipine (Plendil [®]) nifedipine (Adalat [®]) nicardipine (Cardene [®])
Corticosteroids (to treat inflammation or asthma)	dexamethasone (Decadron [®]) fluticasone propionate (Advair Diskus [®] , Cutivate [®] , Flonase [®] , Flovent Diskus [®])
HMG-CoA Reductase Inhibitors (to lower cholesterol levels)	atorvastatin (Lipitor [®]) lovastatin (Mevacor [®]) pravastatin (Pravachol [®]) rosuvastatin (Crestor [®]) simvastatin (Zocor [®])
Immunosuppressants (to prevent organ transplant rejection)	cyclosporine (Sandimmune [®] , Neoral [®]) tacrolimus (Prograf [®]) sirolimus (Rapamune [®])

<u>Type of Drug</u>	<u>Examples of Generic Names (Brand Names)</u>
Narcotic Analgesics	methadone
PDE-5 Inhibitors (to treat erectile dysfunction)	sildenafil (Viagra [®]) vardenafil (Levitra [®]) tadalafil (Cialis [®])
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.

19. 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. The usual dose is 600 mg (two 300 mg tablets or one 600 mg tablet) of PREZISTA, together with 100 mg (one 100 mg capsule) of ritonavir (NORVIR[®]), twice daily *every day*. It may be easier to remember to take PREZISTA and ritonavir (NORVIR[®]) if you take them 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. The type of food is not important. 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.

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.

20. 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.

Your healthcare professional should do blood tests prior to initiating combination treatment including PREZISTA. Patients with liver diseases such as hepatitis B and hepatitis C may have worsening of their liver disease with PREZISTA and may need more frequent monitoring of blood tests. PREZISTA has been reported 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.

Mild to moderate rash has been reported in 7% of subjects receiving PREZISTA. In some patients, PREZISTA has been reported to cause a severe or life-threatening rash. Contact your healthcare provider 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.

As with other protease inhibitors, PREZISTA may cause side effects, including:

- 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. This may happen in patients taking PREZISTA as it has been reported with other protease inhibitor medicines.
- changes in body fat. These changes can happen in patients taking anti-HIV medicines. 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 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, headache, and common cold.

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

21. WHAT DO PREZISTA TABLETS LOOK LIKE?

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

PREZISTA 600 mg tablets are orange, oval-shaped, film-coated tablets mentioning “600” on one side and “” (curved triangle with a dot) on the other side.

22. 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 1-800-325-7504.

Rx Only



Manufactured for Tibotec, Inc. by:
JOLLC, Gurabo, Puerto Rico
Distributed by:

Tibotec Therapeutics, Division of Ortho Biotech Products, L.P., Raritan NJ 08869

© Tibotec, Inc. 2006

Revised: February 2008

10101704