- **are pregnant or planning to become pregnant.** It is not known if APTIVUS can harm your unborn baby. You and your doctor will need to decide if APTIVUS is right for you. If you take APTIVUS while you are pregnant, talk to your doctor about how you can be in the Antiretroviral Pregnancy Registry.

- **are breast-feeding.** Do not breast-feed if you are taking APTIVUS. You should not breast-feed if you have HIV because of the chance of passing the HIV virus to your baby. Talk with your doctor about the best way to feed your baby.

- **are using estrogens for birth control or hormone replacement.** Women who use estrogens for birth control or hormone replacement have an increased chance of developing a skin rash while taking APTIVUS. If a rash occurs, it is usually mild to moderate, but you should talk to your doctor as you may need to temporarily stop taking either APTIVUS or the other medicine that contains estrogen or female hormones.

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

- Some medicines cannot be taken at all with APTIVUS
- Some medicines will require a change in dosage if taken with APTIVUS
- Some medicines will require close monitoring if taken with APTIVUS.

Women taking birth control pills need to use another birth control method. APTIVUS makes birth control pills work less well.

Know all the medicines you take and keep a list of them with you. Show this list to all your doctors and pharmacists anytime you get a new medicine you take. They will tell you if you can take these other medicines with APTIVUS. **Do not start any new medicines while you are taking APTIVUS without first talking with your doctor or pharmacist.** You can ask your doctor or pharmacist for a list of medicines that can interact with APTIVUS.

How should I take APTIVUS?

- Take APTIVUS exactly as your doctor has prescribed. You should check with your doctor or pharmacist if you are not sure. **You must take APTIVUS at the same time as NORVIR® (ritonavir).** The usual dose is 500 mg (two 250 mg capsules) of APTIVUS, together with 200 mg (two 100 mg capsules or 2.5 mL of solution) of NORVIR, twice per day. APTIVUS with NORVIR must be used together with other anti-HIV medicines.

APTIVUS comes in a capsule form and you should **swallow APTIVUS capsules whole. Do not chew the capsules.**

- Always take APTIVUS with food.
- Do not change your dose or stop taking APTIVUS without first talking with your doctor.
- If you take too much APTIVUS, call your doctor or poison control center right away.
- If you forget to take APTIVUS, take the next dose of APTIVUS, together with NORVIR® (ritonavir), as soon as possible. Do not take a double dose to make up for a missed dose.

- It is very important to take all your anti-HIV medicines as prescribed and at the right times of day. This can help your medicines work better. It also lowers the chance that your medicines will stop working to fight HIV (drug resistance).
- When your APTIVUS supply starts to run low, get more from your doctor or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short period of time. The HIV virus may develop resistance to APTIVUS and become harder to treat. You should NEVER stop taking APTIVUS or your other HIV medicines without talking with your doctor.

What are the possible side effects of APTIVUS?

APTIVUS may cause serious side effects, including:

- **liver problems, including liver failure and death.** Your doctor should do blood tests to monitor your liver function during treatment with APTIVUS. Patients with liver diseases such as Hepatitis B and Hepatitis C may have worsening of their liver disease with APTIVUS and should have more frequent monitoring blood tests.

- **rash.** Mild to moderate rash, including flat or raised rashes or sensitivity to the sun, have been reported in approximately 10% of subjects receiving APTIVUS. Some patients who developed rash also had joint pain or stiffness, throat tightness, or generalized itching.

- **increased bleeding in patients with hemophilia.** This can happen in patients taking APTIVUS or other protease inhibitor medicines.

- **diabetes and high blood sugar (hyperglycemia).** This can happen in patients taking APTIVUS or other protease inhibitor medicines. Some patients have diabetes before starting treatment with APTIVUS which gets worse. Some patients get diabetes during treatment with APTIVUS. Some patients will need changes in their diabetes medicine. Some patients will need new diabetes medicine.

- **increased blood fat (lipid) levels.** Your doctor should do blood tests to monitor your blood fat (triglycerides and cholesterol) during treatment with APTIVUS. Some patients taking APTIVUS have large increases in triglycerides and cholesterol. The long-term chance of having a heart attack or stroke due to increases in blood fats caused by APTIVUS is not known at this time.

- **changes in body fat.** These changes have happened in patients taking APTIVUS. and other anti-HIV medicines. The changes may include an increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the back, chest, and stomach area. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known.

The most common side effects include diarrhea, nausea, vomiting, stomach pain, tiredness and headache. Women taking birth control pills may get a skin rash.

It may be hard to tell the difference between side effects caused by APTIVUS, by the other medicines you are also taking, or by the complications of HIV infection. For this reason it is very important that

you tell your doctor about any changes in your health. You should report any new or continuing symptoms to your doctor right away. Your doctor may be able to help you manage these side effects.

The list of side effects is **not** complete. Ask your doctor or pharmacist for more information.

How should I store APTIVUS?

- Store APTIVUS capsules in a refrigerator at approximately **36°F to 46°F (2°C to 8°C).** Once the bottle is opened, the contents must be used within 60 days. Patients may take the bottle with them for use away from home so long as the bottle remains at a temperature of approximately **59°F to 86°F (15°C to 30°C).** You can write the date of opening the bottle on the label. Do not use after the expiration date written on the bottle.

- **Keep APTIVUS and all medicines out of the reach of children.**

General advice about APTIVUS

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use APTIVUS for a condition for which it was not prescribed. Do not give APTIVUS to other people, even if they have the same condition you have. It may harm them.

This leaflet summarizes the most important information about APTIVUS. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about APTIVUS that is written for health professionals.

For additional information, you may also call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257, or (TTY) 1-800-459-9906. You may also request information through the company website at http://us.boehringer-ingelheim.com.

What are the ingredients in APTIVUS?

Active Ingredient: tipranavir

Major Inactive Ingredients: dehydrated alcohol, polyoxyl 35 castor oil, propylene glycol, mono/diglycerides of caprylic/capric acid and gelatin.

Rx only

Distributed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

APTIVUS is a registered trademark used under license from Boehringer Ingelheim International GmbH

APTIVUS Capsules are covered by U.S. Patents 5,852,195, 6,147,095, 6,169,181 and 6,231,887

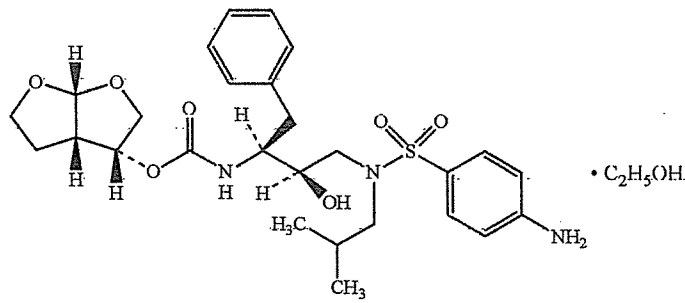
PREZISTA™* (Tibotec, Inc.)
(darunavir)

Tablets

DESCRIPTION

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

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



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

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

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

MICROBIOLOGY

Mechanism of Action

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

Antiviral Activity

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

Resistance

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

Clinical studies of darunavir/ritonavir in treatment-experienced subjects

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

Cross-resistance

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

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

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

Baseline Genotype/Phenotype and Virologic Outcome Analyses

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

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

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

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

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

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

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

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

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

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults

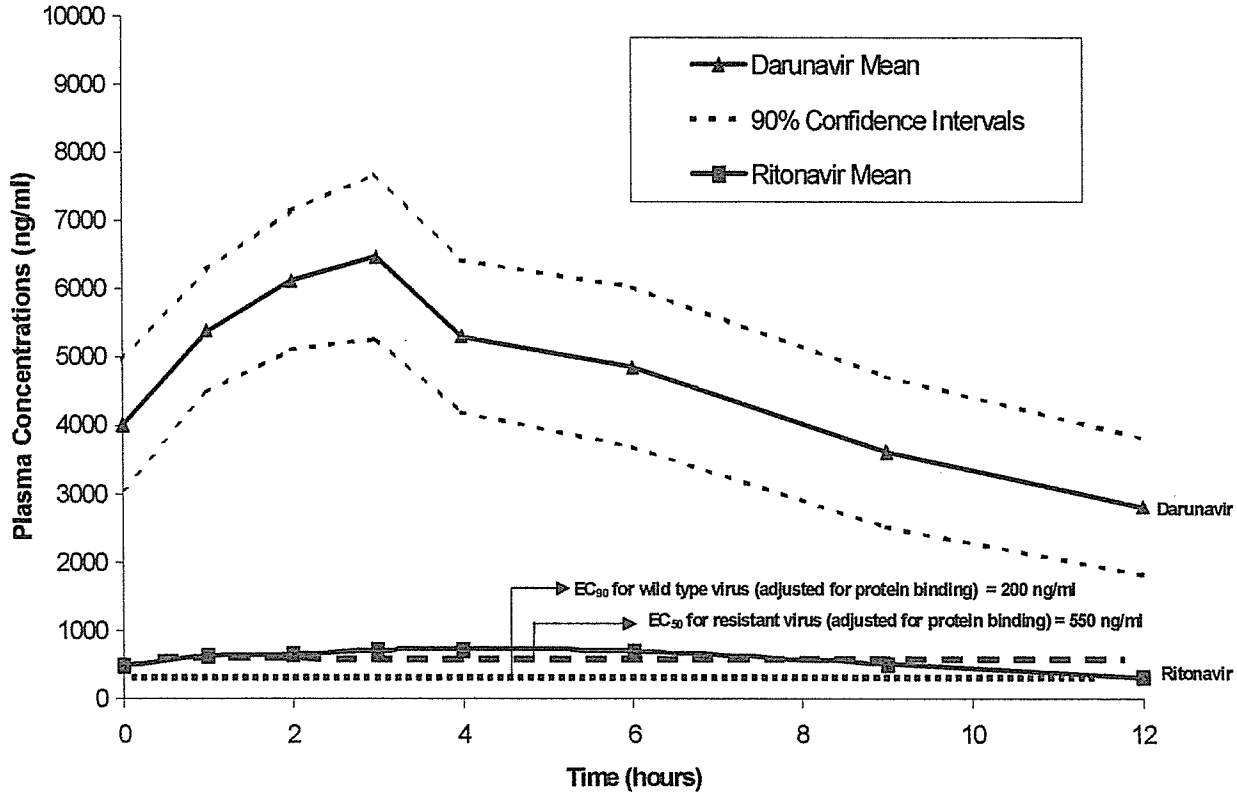
The pharmacokinetics of darunavir, co-administered with low dose ritonavir (100 mg twice daily), have been evaluated in healthy adult volunteers and in HIV-1 infected subjects. Table 3 displays the population pharmacokinetic estimates of darunavir from an analysis of integrated data from Studies TMC114-C213 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 <u>Co-administered Drugs</u> in the Presence of Darunavir/Ritonavir**						
					LS Mean Ratio % (90% CI) of <u>Co-Administered Drug</u> Pharmacokinetic Parameters With/Without Darunavir No effect =1.00		
	Dose/Schedule						
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.