HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PREZISTA safely and effectively. See Full Prescribing Information for PREZISTA.

PREZISTA® (darunavir) Tablet, Film Coated for Oral use

Initial U.S. Approval – 2006

----------RECENT MAJOR CHANGES----------

- Indications and Usage (1) 10/2008
- Dosage and Administration (2) 10/2008
- Contraindications (4) 10/2008
- Warnings and Precautions (5) 10/2008

----------INDICATIONS AND USAGE----------

PREZISTA is a human immunodeficiency virus (HIV-1) protease inhibitor indicated for the treatment of HIV infection in adult patients. PREZISTA must be co-administered with 100 mg ritonavir (PREZISTA/rtv) and with other antiretroviral agents. (1)

----------DOSAGE AND ADMINISTRATION----------

- Treatment-naïve adult patients: 800 mg (two 400 mg tablets) taken with ritonavir 100 mg once daily and with food. (2.1)
- Treatment-experienced adult patients: 600 mg (one 600 mg tablet or two 300 mg tablets) taken with ritonavir 100 mg twice daily and with food. (2.1)
- PREZISTA/rtv is not recommended for use in patients with severe hepatic impairment. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

300 mg tablets, 400 mg tablets, and 600 mg tablets (3)

----------CONTRAINDICATIONS----------

Co-administration with dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, pimozide, oral midazolam, triazolam, St. Johns Wort, lovastatin, simvastatin, rifampin. (4)

- 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.

----------WARNINGS AND PRECAUTIONS----------

- Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported with PREZISTA/rtv. Monitor liver function before and during therapy, especially in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases. (5.2, 6)
- Skin rashes ranging from mild to severe, including Stevens-Johnson Syndrome, have been reported. Discontinue treatment if severe rash develops. (5.3, 6)
- Use with caution in patients with a known sulfonamide allergy. (5.4)
- Patients may develop new onset diabetes mellitus or hyperglycemia. Initiation or dose adjustments of insulin or oral hypoglycemic agents may be required. (5.6)
- Patients may develop redistribution/accumulation of body fat (5.7) or immune reconstitution syndrome. (5.8)
- Patients with hemophilia may develop increased bleeding events. (5.9)

----------ADVERSE REACTIONS----------

- The most common adverse drug reactions to PREZISTA/rtv (incidence ≥ 5%) of at least moderate intensity (≥ Grade 2) were diarrhea, nausea, headache and abdominal pain. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Tibotec Therapeutics at 1-877-REACH-TT or 1-877-732-2488 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Co-administration of PREZISTA/ritonavir with other drugs can alter the concentration of other drugs and other drugs may alter the concentrations of darunavir. The potential drug-drug concentrations must be considered prior to and during therapy. (4, 5.5, 7, 12.3).

----------USE IN SPECIFIC POPULATIONS----------

- Use during pregnancy only if the potential benefit justifies the potential risk. (8.1)
  - An Antiviral Pregnancy Registry has been established. Register patients by calling 1-800-258-4263.
- Mothers should be instructed not to breastfeed due to the potential for HIV transmission and the potential for serious adverse reactions in nursing infants. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: 10/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

[*Sections or subsections omitted from the Full Prescribing Information are not listed]

FULL PRESCRIBING INFORMATION

1 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-1) infection.

This indication is based on analyses of plasma HIV RNA levels and CD4+ cell counts from 2 controlled Phase 3 trials of 48 weeks duration in antiretroviral treatment-naïve and treatment-experienced patients and 2 controlled Phase 2 trials of 96 weeks duration in clinically advanced, treatment-experienced patients.

In treatment-experienced patients, 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 Clinical Pharmacology (12.4)*].
- The use of other active agents with PREZISTA/rtv is associated with a greater likelihood of treatment response [*see Clinical Pharmacology (12.4) and Clinical Studies (14.3)*].

The risks and benefits of PREZISTA/rtv have not been established in pediatric patients.

No clinical studies have demonstrated the effect of PREZISTA/rtv on clinical progression of HIV-1.

2 DOSAGE AND ADMINISTRATION

2.1 Adult Patients

Treatment-Naïve Adult Patients

The recommended oral dose of PREZISTA tablets is 800 mg (two 400 mg tablets) taken with ritonavir 100 mg once daily and with food. The type of food does not affect exposure to darunavir.

Treatment-Experienced Adult Patients

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

2.2 Pediatric Patients

The safety and efficacy of PREZISTA in pediatric patients has not been established [*see Use in Specific Populations (8.4) and Clinical Pharmacology (12.3)*].

2.3 Patients with Hepatic Impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment. No data are available 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 Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

3.1 PREZISTA 300 mg Tablets

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.

3.2 PREZISTA 400 mg Tablets

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

3.3 PREZISTA 600 mg Tablets

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

4 CONTRAINDICATIONS

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 and other contraindicated drugs (which may lead to reduced efficacy of darunavir) are listed in Table 1 [*also see Drug Interactions (7.3)*, Table 6].

Table 1: Drugs That Are Contraindicated With PREZISTA/rtv

Drug Class	Drugs Within Class That Are Contraindicated With PREZISTA/rtv	Clinical Comment
Ergot Derivatives	Dihydroergotamine, Ergonovine, Ergotamine, Methylergonovine	Potential for serious and/or life-threatening events such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent	Cisapride	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Neuroleptic	Pimozide	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Sedative/hypnotics	Orally administered Midazolam, Triazolam	Triazolam and orally administered midazolam are extensively metabolized by CYP3A. Co-administration of triazolam or orally administered midazolam with PREZISTA/rtv may cause large increases in the concentrations of these benzodiazepines. Potential for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression.
Herbal Products	St. John's Wort (*Hypericum perforatum*)	Patients taking PREZISTA/rtv should not use products containing St. John's wort because co-administration may result in reduced plasma concentrations of darunavir. This may result in loss of therapeutic effect and development of resistance.
HMG CoA Reductase Inhibitors	Lovastatin, Simvastatin	Potential for serious reactions such as myopathy including rhabdomyolysis.

		For dosing recommendation regarding atorvastatin and pravastatin, see Table 6: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction.
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.

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.

5 WARNINGS AND PRECAUTIONS

5.1 General

PREZISTA must be co-administered with ritonavir and food to achieve the desired antiviral effect. Failure to administer PREZISTA with ritonavir and food may result in a loss of efficacy of darunavir.

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

5.2 Hepatotoxicity

Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported with PREZISTA/rtv. During the clinical development program (N=3063), hepatitis was 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.

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 should prompt consideration of interruption or discontinuation of treatment.

5.3 Skin Rash

In clinical trials (n=3063), rash (all grades, regardless of causality) occurred in 10.3% of subjects treated with PREZISTA [*also see Adverse Reactions* (6)]. Rash was mostly mild-to-moderate, often occurring within the first four weeks of treatment and resolving with continued dosing. The discontinuation rate due to rash in subjects using PREZISTA/rtv was 0.5%.

Severe skin rash, accompanied by fever and/or elevations of transaminases in some cases, has been reported in 0.4% of subjects. Stevens-Johnson Syndrome has been rarely (<0.1%) reported. Treatment with PREZISTA should be discontinued if severe rash develops.

5.4 Sulfa Allergy

Darunavir contains a sulfonamide moiety. PREZISTA should be used with caution in patients with a known sulfonamide allergy. In clinical studies with PREZISTA/rtv, the incidence and severity of rash was similar in subjects with or without a history of sulfonamide allergy.

5.5 Drug Interactions

See Table 1 for a listing of drugs that are contraindicated for use with PREZISTA/rtv due to potentially life-threatening adverse events, significant drug-drug interactions, or loss of therapeutic effect to PREZISTA [*see Contraindications (4)*]. Please refer to Table 6 for established and other potentially significant drug-drug interactions [*see Drug Interactions (7.3)*].

5.6 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 (PI) 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 PI 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 PI therapy and these events have not been established.

5.7 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.

5.8 Immune Reconstitution Syndrome

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

5.9 Hemophilia

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

5.10 Resistance/Cross-Resistance

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

6 ADVERSE REACTIONS

The safety assessment is based on all safety data from the Phase 2b studies (Studies TMC114-C213, TMC114-C202, TMC114-C215, and TMC114-C208) and Phase 3 studies (TMC114-C211, TMC114-C214, TMC114-C209, DUET-1 (TMC125-C206), and DUET-2 (TMC125-C216)) reported with PREZISTA/rtv in a total of 3063 subjects.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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.

6.1 Antiretroviral Treatment-Naïve Adult Subjects

Study TMC114-C211

The safety assessment is based on all safety data from the Phase 3 trial TMC114-C211 comparing PREZISTA/rtv 800/100 mg once daily versus lopinavir/ritonavir 800/200 mg per day in 689 antiretroviral treatment-naïve HIV-1-infected adult subjects. The total mean exposure for subjects in the PREZISTA/rtv 800/100 mg once daily arm and in the lopinavir/ritonavir 800/200 mg per day arm was 54.8 and 53.3 weeks, respectively.

The majority of the adverse drug reactions (ADRs) reported during treatment with PREZISTA/rtv 800/100 mg once daily were mild in severity. The most common ADRs to PREZISTA/rtv 800/100 mg once daily (≥ 5%) of at least moderate intensity (≥ Grade 2) were diarrhea and headache. 2% of subjects in the PREZISTA/rtv arm discontinued treatment due to ADRs.

ADRs to PREZISTA/rtv 800/100 mg once daily of at least moderate intensity (≥ Grade 2) in antiretroviral treatment naïve HIV-1-infected adult subjects are presented in Table 2.

Table 2: Selected Adverse Drug Reactions to PREZISTA/rtv 800/100 mg Once Daily* of At Least Moderate Intensity (≥ Grade 2) in Antiretroviral Treatment-Naïve HIV-1-Infected Adult Subjects

	Randomized Study TMC114-C211	
System Organ Class, Preferred Term, %	**PREZISTA/rtv 800/100 mg once daily + TDF/FTC N = 343**	**lopinavir/ritonavir 800/200 mg per day + TDF/FTC N = 346**
Gastrointestinal Disorders		
Abdominal pain	4%	5%
Acute pancreatitis	< 1%	< 1%
Diarrhea	6%	13%
Dyspepsia	< 1%	0%
Flatulence	< 1%	< 1%
Nausea	3%	3%
Vomiting	2%	3%
General Disorders and Administration Site Conditions		
Asthenia	< 1%	0%
Fatigue	< 1%	2%
Hepatobiliary Disorders		
Acute Hepatitis (e.g., acute hepatitis, cytolytic hepatitis, hepatotoxicity)	< 1%	< 1%
Metabolism and Nutrition Disorders		
Anorexia	1%	< 1%
Diabetes mellitus	< 1%	< 1%
Musculoskeletal and Connective Tissue Disorders		
Myalgia	< 1%	< 1%

Nervous System Disorders		
Headache	5%	4%
Psychiatric Disorders		
Abnormal dreams	< 1%	< 1%
Skin and Subcutaneous Tissue Disorders		
Pruritus	< 1%	< 1%
Rash	2%	4%
Stevens-Johnson Syndrome	< 1%	0%
N=total number of subjects per treatment group TDF = tenofovir disoproxil fumarate FTC = emtricitabine * Excluding laboratory abnormalities reported as ADRs		

Laboratory abnormalities:
The percentages of antiretroviral treatment-naïve HIV-1-infected adult subjects treated with PREZISTA/rtv 800/100 mg once daily with Grade 2 to 4 laboratory abnormalities, considered ADRs, are presented in Table 3.

Table 3: Grade 2 to 4 Laboratory Abnormalities Observed in Antiretroviral Treatment-Naïve HIV-1-Infected Adult Subjects*

		Randomized Study TMC114-C211	
Laboratory Parameter Preferred Term, %	**Limit**	**PREZISTA/rtv 800/100 mg once daily + TDF/FTC N = 343**	**lopinavir/ritonavir 800/200 mg per day + TDF/FTC N = 346**
Biochemistry			
Alanine Aminotransferase			
Grade 2	> 2.5 to ≤ 5.0 X ULN	5%	5%
Grade 3	> 5.0 to ≤ 10.0 X ULN	3%	2%
Grade 4	> 10.0 X ULN	< 1%	3%
Aspartate Aminotransferase			
Grade 2	> 2.5 to ≤ 5.0 X ULN	6%	6%
Grade 3	> 5.0 to ≤ 10.0 X ULN	3%	2%
Grade 4	> 10.0 X ULN	< 1%	2%
Alkaline Phosphatase			
Grade 2	> 2.5 to ≤ 5.0 X ULN	1%	< 1%
Grade 3	> 5.0 to ≤ 10.0 X ULN	0%	< 1%
Grade 4	> 10.0 X ULN	0%	0%
Hyperbilirubinemia			
Grade 2	> 1.5 to ≤ 2.5 X ULN	< 1%	3%
Grade 3	> 2.5 to ≤ 5.0 X ULN	0%	< 1%
Grade 4	> 5.0 X ULN	0%	0%
Triglycerides			
Grade 2	5.65-8.48 mmol/L 500-750 mg/dL	2%	6%
Grade 3	8.49-13.56 mmol/L 751-1200 mg/dL	1%	4%
Grade 4	> 13.56 mmol/L > 1200 mg/dL	< 1%	< 1%
Total Cholesterol			
Grade 2	6.20-7.77 mmol/L 240-300 mg/dL	12%	19%
Grade 3	> 7.77 mmol/L	1%	4%

	> 300 mg/dL		
Low-Density Lipoprotein Cholesterol			
Grade 2	4.13-4.90 mmol/L 160-190 mg/dL	11%	6%
Grade 3	≥ 4.91 mmol/L ≥ 191 mg/dL	2%	4%
Elevated Glucose Levels			
Grade 2	6.95-13.88 mmol/L 126-250 mg/dL	6%	7%
Grade 3	13.89-27.75 mmol/L 251-500 mg/dL	< 1%	0%
Grade 4	> 27.75 mmol/L > 500 mg/dL	0%	0%
Pancreatic Lipase			
Grade 2	> 1.5 to ≤ 3.0 X ULN	2%	< 1%
Grade 3	> 3.0 to ≤ 5.0 X ULN	< 1%	< 1%
Grade 4	> 5.0 X ULN	0%	< 1%
Pancreatic Amylase			
Grade 2	> 1.5 to ≤ 2.0 X ULN	4%	2%
Grade 3	> 2.0 to ≤ 5.0 X ULN	3%	3%
Grade 4	> 5.0 X ULN	0%	< 1%
N=total number of subjects per treatment group TDF = tenofovir disoproxil fumarate FTC = emtricitabine * Grade 4 data not applicable in Division of AIDS grading scale.			

6.2 Antiretroviral Treatment-Experienced Adult Subjects

Study TMC114-C214

The safety assessment is based on all safety data from the Phase 3 trial TMC114-C214 comparing PREZISTA/rtv 600/100 mg twice daily versus lopinavir/ritonavir 400/100 mg twice daily in 595 antiretroviral treatment-experienced HIV-1-infected adult subjects. The total mean exposure for subjects in the PREZISTA/rtv 600/100 mg twice daily arm and in the lopinavir/ritonavir 400/100 mg twice daily arm was 53.5 and 51.5 weeks, respectively.

The majority of the ADRs reported during treatment with PREZISTA/rtv 600/100 mg twice daily were mild in severity. The most common ADRs to PREZISTA/rtv 600/100 mg twice daily (≥ 5%) of at least moderate intensity (≥ Grade 2) were diarrhea, nausea, rash, and abdominal pain. 3.7% of subjects in the PREZISTA/rtv arm discontinued treatment due to ADRs.

ADRs to PREZISTA/rtv 600/100 mg twice daily of at least moderate intensity (≥ Grade 2) in antiretroviral treatment-experienced HIV-1-infected adult subjects are presented in Table 4.

Table 4: Selected Adverse Drug Reactions to PREZISTA/rtv 600/100 mg Twice Daily* of At Least Moderate Intensity (≥ Grade 2) in Antiretroviral Treatment-Experienced HIV-1-Infected Adult Subjects

	Randomized Study TMC114-C214	
System Organ Class, Preferred Term, %	**PREZISTA/rtv 600/100 mg twice daily + OBR N = 298**	**lopinavir/ritonavir 400/100 mg twice daily + OBR N = 297**
Gastrointestinal Disorders		
Abdominal distension	2%	< 1%
Abdominal pain	5%	2%

Diarrhea	12%	18%
Dyspepsia	2%	< 1%
Flatulence	< 1%	1%
Nausea	7%	6%
Vomiting	4%	3%
General Disorders and Administration Site Conditions		
Asthenia	3%	1%
Fatigue	1%	1%
Metabolism and Nutrition Disorders		
Anorexia	1%	2%
Diabetes mellitus	< 1%	0%
Musculoskeletal and Connective Tissue Disorders		
Myalgia	1%	< 1%
Nervous System Disorders		
Headache	2%	3%
Psychiatric Disorders		
Abnormal dreams	< 1	0%
Skin and Subcutaneous Tissue Disorders		
Pruritus	< 1%	1%
Rash	6%	3%
N=total number of subjects per treatment group OBR = optimized background regimen * Excluding laboratory abnormalities reported as ADRs		

Laboratory abnormalities:
The percentages of antiretroviral treatment-experienced HIV-1-infected adult subjects treated with PREZISTA/rtv 600/100 mg twice daily with Grade 2 to 4 laboratory abnormalities, considered ADRs, are presented in Table 5.

Table 5: Grade 2 to 4 Laboratory Abnormalities Observed in Antiretroviral Treatment-Experienced HIV-1-Infected Adult Subjects*

		Randomized Study TMC114-C214	
Laboratory Parameter Preferred Term, %	**Limit**	**PREZISTA/rtv 600/100 mg twice daily + OBR N = 298**	**lopinavir/ritonavir 400/100 mg twice daily + OBR N = 297**
Biochemistry			
Alanine Aminotransferase			
Grade 2	> 2.5 to ≤ 5.0 X ULN	6%	5%
Grade 3	> 5.0 to ≤ 10.0 X ULN	2%	2%
Grade 4	> 10.0 X ULN	1%	2%
Aspartate Aminotransferase			
Grade 2	> 2.5 to ≤ 5.0 X ULN	4%	6%
Grade 3	> 5.0 to ≤ 10.0 X ULN	2%	2%
Grade 4	> 10.0 X ULN	< 1%	2%
Alkaline Phosphatase			
Grade 2	> 2.5 to ≤ 5.0 X ULN	< 1%	0%
Grade 3	> 5.0 to ≤ 10.0 X ULN	< 1%	< 1%
Grade 4	> 10.0 X ULN	0%	0%
Hyperbilirubinemia			
Grade 2	> 1.5 to ≤ 2.5 X ULN	0%	1%
Grade 3	> 2.5 to ≤ 5.0 X ULN	< 1%	0%
Grade 4	> 5.0 X ULN	< 1%	0%

Triglycerides			
Grade 2	5.65-8.48 mmol/L 500-750 mg/dL	11%	11%
Grade 3	8.49-13.56 mmol/L 751-1200 mg/dL	7%	9%
Grade 4	> 13.56 mmol/L > 1200 mg/dL	2%	5%
Total Cholesterol			
Grade 2	6.20-7.77 mmol/L 240-300 mg/dL	24%	19%
Grade 3	> 7.77 mmol/L > 300 mg/dL	8%	11%
Low-Density Lipoprotein Cholesterol			
Grade 2	4.13-4.90 mmol/L 160-190 mg/dL	13%	11%
Grade 3	≥ 4.91 mmol/L ≥ 191 mg/dL	7%	8%
Elevated Glucose Levels			
Grade 2	6.95-13.88 mmol/L 126-250 mg/dL	8%	9%
Grade 3	13.89-27.75 mmol/L 251-500 mg/dL	< 1%	< 1%
Grade 4	> 27.75 mmol/L > 500 mg/dL	< 1%	0%
Pancreatic Lipase			
Grade 2	> 1.5 to ≤ 3.0 X ULN	2%	4%
Grade 3	> 3.0 to ≤ 5.0 X ULN	2%	< 1%
Grade 4	> 5.0 X ULN	< 1%	0%
Pancreatic Amylase			
Grade 2	> 1.5 to ≤ 2.0 X ULN	6%	6%
Grade 3	> 2.0 to ≤ 5.0 X ULN	6%	3%
Grade 4	> 5.0 X ULN	0%	0%
N=total number of subjects per treatment group OBR = optimized background regimen * Grade 4 data not applicable in Division of AIDS grading scale.			

6.3 Serious ADRs

The following serious ADRs of at least moderate intensity (≥ Grade 2) occurred in the Phase 2b studies (Studies TMC114-C213, TMC114-C202, TMC114-C215, and TMC114-C208) and Phase 3 studies (TMC114-C211, TMC114-C214, TMC114-C209, DUET-1 (TMC125-C206), and DUET-2 (TMC125-C216)) with PREZISTA/rtv: abdominal pain, acute hepatitis, acute pancreatitis, anorexia, asthenia, diabetes mellitus, diarrhea, fatigue, headache, hepatic enzyme increased, hypercholesterolemia, hyperglycemia, hypertriglyceridemia, immune reconstitution syndrome, low density lipoprotein increased, nausea, pancreatic enzyme increased, rash, Stevens-Johnson Syndrome, and vomiting.

6.4 Additional ADRs to PREZISTA/rtv identified in other clinical trials

In Studies TMC114-C213, TMC114-C202, TMC114-C215, TMC114-C208, TMC114-C209, DUET-1, and DUET-2, the only additional ADR of interest identified was lipodystrophy.

6.5 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 and Precautions (5.2)*]. The pharmacokinetic exposure in co-infected subjects was comparable to that in subjects without co-infection.

6.6 Postmarketing Experience

The following events have been identified during postmarketing use of PREZISTA. Because these events are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Rarely, events of hypersensitivity (including facial edema), and rhabdomyolysis (associated with co-administration with HMG-CoA reductase inhibitors and PREZISTA) have been reported.

7 DRUG INTERACTIONS

See also *Contraindications (4)* and *Clinical Pharmacology (12.3)*.

7.1 Potential for PREZISTA/rtv to Affect Other Drugs

PREZISTA co-administered with ritonavir is an inhibitor of CYP3A and CYP2D6. Co-administration of PREZISTA and ritonavir with drugs that are primarily metabolized by CYP3A and CYP2D6 may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse events (see Table 6).

7.2 Potential for Other Drugs to Affect Darunavir

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 (see Table 6).

7.3 Established and Other Potentially Significant Drug Interactions

Table 6 provides dosing recommendations as a result of drug interactions with PREZISTA/rtv. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy.

Table 6: 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 (12.3)* for Magnitude of Interaction, Tables 8 and 9]

Concomitant Drug Class: Drug Name	**Effect on Concentration of Darunavir or Concomitant Drug**	**Clinical Comment**
HIV-Antiviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
didanosine	↔ darunavir ↔ didanosine	Didanosine should be administered one hour before or two hours after PREZISTA/rtv (which are administered with food).
HIV-Antiviral Agents: HIV-Protease Inhibitors (PIs)		
indinavir	↑ darunavir	The appropriate dose of indinavir in

(The reference regimen for indinavir was indinavir/ritonavir 800/100 mg twice daily.)	↑ indinavir	combination with PREZISTA/rtv has not been established.
lopinavir/ritonavir	↓ darunavir ↔ lopinavir	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-dose of ritonavir.
saquinavir	↓ darunavir ↔ saquinavir	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, flecainide, propafenone digoxin	↑ antiarrhythmics ↑ digoxin	Concentrations of these drugs 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. 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 are decreased when co-administered with PREZISTA/rtv. It is recommended that the international normalized ratio (INR) be monitored when warfarin is combined with PREZISTA/rtv.
Anticonvulsant: carbamazepine	↔ darunavir ↑ carbamazepine	The dose of either darunavir/ritonavir or carbamazepine does not need to be adjusted when initiating co-administration with darunavir/ritonavir and carbamazepine. Clinical monitoring of carbamazepine concentrations and its dose titration is recommended to achieve the desired clinical response.
Anticonvulsant: phenobarbital, phenytoin	↔ darunavir ↓ phenytoin ↓ phenobarbital	Co-administration of PREZISTA/rtv may cause decrease in the steady-state concentrations of phenytoin and phenobarbital. Phenytoin and phenobarbital levels should be monitored when co-administering with PREZISTA/rtv.
Antidepressant:	↑ trazodone	Concomitant use of trazodone or

trazodone, desipramine	↑ desipramine	desipramine and PREZISTA/rtv may increase plasma concentrations of trazodone or desipramine which may lead to adverse events such as nausea, dizziness, hypotension and syncope. If trazodone or desipramine is used with PREZISTA/rtv, the combination should be used with caution and a lower dose of trazodone or desipramine should be considered.
Anti-infective: clarithromycin	↔ darunavir ↑ clarithromycin	No dose adjustment of the combination is required for patients with normal renal function. For patients with renal impairment, the following dose adjustments should be considered: • 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 (not studied)	Ketoconazole and itraconazole are potent inhibitors as well as substrates of CYP3A. Concomitant systemic use of ketoconazole, itraconazole, and darunavir/ritonavir may increase plasma concentration of darunavir. 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. Plasma concentrations of voriconazole may be decreased in the presence of darunavir/ritonavir. Voriconazole should not be administered to patients receiving darunavir/ritonavir unless an assessment of the benefit/risk ratio justifies the use of voriconazole.
Antimycobacterial: rifabutin The reference regimen for rifabutin was 300 mg once daily	↑ darunavir ↑ rifabutin ↑ 25-*O*-desacetylrifabutin	Dose reduction of rifabutin by at least 75% of the usual dose (300 mg once daily) is recommended (i.e., a maximum dose of 150 mg every other day). Increased monitoring for adverse events is warranted in patients receiving this combination and further dose reduction of rifabutin may be necessary.
β-Blockers:	↑ beta-blockers	Caution is warranted and clinical

metoprolol, timolol		monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with PREZISTA/rtv.
Benzodiazepines: parenterally administered midazolam	↑ midazolam	Concomitant use of parenteral midazolam with PREZISTA/rtv may increase plasma concentrations of midazolam. Co-administration should be done in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dosage reduction for midazolam should be considered, especially if more than a single dose of midazolam is administered. Co-administration of oral midazolam with PREZISTA/rtv is CONTRAINDICATED.
Calcium Channel Blockers: felodipine, nifedipine, nicardipine	↑ calcium channel blockers	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.
Corticosteroid: **Systemic**: dexamethasone	↓ darunavir	Systemic dexamethasone induces CYP3A and can thereby decrease darunavir plasma concentrations. This may result in loss of therapeutic effect to PREZISTA.
Corticosteroid: **Inhaled/Nasal**: fluticasone propionate	↑ fluticasone propionate	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.
HMG-CoA Reductase Inhibitors: pravastatin, atorvastatin, rosuvastatin	↑ pravastatin ↑ atorvastatin ↑ rosuvastatin	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.
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 when co-administered with PREZISTA/rtv.
Narcotic Analgesic: methadone	↓ methadone	No adjustment of methadone dosage is required when initiating co-

		administration of PREZISTA/rtv. However, clinical monitoring is recommended as the dose of methadone during maintenance therapy may need to be adjusted in some patients.
Neuroleptics: risperidone, thioridazine	↑ neuroleptics	A dose decrease may be needed for these drugs when co-administered with PREZISTA/rtv.
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	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 can be used with increased monitoring for PDE-5 inhibitor-associated adverse events.
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.

In addition to the drugs included in Table 6, the interaction between PREZISTA/rtv and the following drugs were evaluated in clinical studies and no dose adjustments are needed for either drug [see *Clinical Pharmacology (12.3)*]: atazanavir, efavirenz, etravirine, nevirapine, omeprazole, ranitidine, and tenofovir disoproxil fumarate.

Other nucleoside reverse transcriptase inhibitors (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 PIs:
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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: PREZISTA should be used during pregnancy only if the potential benefit justifies the potential risk.

No adequate and well-controlled studies have been conducted in pregnant women. Reproduction studies conducted with darunavir showed no embryotoxicity or teratogenicity in mice, rats and rabbits. However, due to limited bioavailability and/or dosing limitations, animal exposures (based on AUC) were only 50% (mice and rats) and 5% (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 and mating performance of offspring were 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.

In the juvenile toxicity study where rats were directly dosed with darunavir, deaths occurred from post-natal day 5 through 11 at plasma exposure levels ranging from 0.1 to 1.0 of the human exposure levels. In a 4-week rat toxicology study, when dosing was initiated on post-natal day 23 (the human equivalent of 2 to 3 years of age), no deaths were observed with a plasma exposure (in combination with ritonavir) of 0.1 of the human plasma exposure levels.

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.*

8.3 Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-infected mothers in the United States 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**.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

PREZISTA/rtv should not be used in pediatric patients below 3 years of age in view of toxicity and mortality observed in juvenile rats dosed with darunavir (from 20 mg/kg to 1000 mg/kg) up to days 23 to 26 of age [*see Use in Specific Populations (8.1), Clinical Pharmacology (12.3) and Nonclinical Toxicology (13.2)*].

8.5 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 [*see Clinical Pharmacology (12.3)*].

8.6 Hepatic Impairment

No dose adjustment of PREZISTA/rtv is necessary for patients with either mild or moderate hepatic impairment. No pharmacokinetic or safety data are available regarding the use of PREZISTA/rtv in subjects with severe hepatic impairment, therefore, PREZISTA/rtv is not recommended for use in patients with severe hepatic impairment [*see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)*].

8.7 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). No pharmacokinetic data are available in HIV-1-infected patients with severe renal impairment or end stage renal disease; however, because 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 (12.3)*].

10 OVERDOSAGE

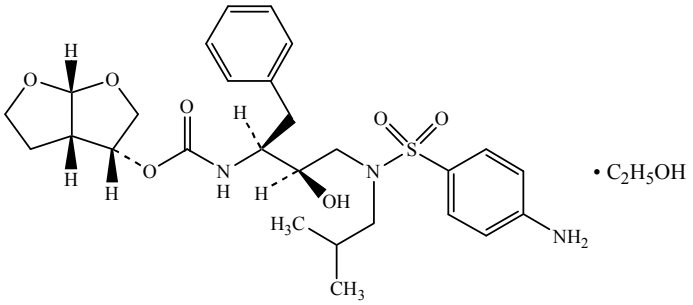
Human experience of acute overdose with PREZISTA/rtv is limited. Single doses up to 3200 mg of the oral solution of darunavir alone and up to 1600 mg of the tablet formulation of darunavir in combination with ritonavir have been administered to healthy volunteers without untoward symptomatic effects.

No specific antidote is available 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.

11 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 $C_{27}H_{37}N_3O_7S \bullet C_2H_5OH$ 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. PREZISTA 400 mg is available as a light orange, oval-shaped, film-coated tablet for oral administration. Each 300 mg tablet contains darunavir ethanolate equivalent to 300 mg of darunavir. Each 400 mg tablet contains darunavir ethanolate equivalent to 400 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Darunavir is an HIV antiviral drug [*see Clinical Pharmacology (12.4)*].

12.2 Pharmacodynamics

In an open-label, randomized, placebo- and active-controlled, four-way crossover trial, 40 healthy subjects were administered supratheraputic doses of darunavir/ritonavir 1600/100 mg once daily and 800/100 mg twice daily for seven days.

At the mean maximum darunavir concentration of 6599 ng/mL observed in this study, the mean increase in QTcF was 2.2 ms with a 90% two-sided confidence interval (CI) of -2.0 to 6.3 ms. When evaluating the 2-sided 90% CI on the time-matched mean changes in QTcF versus placebo control, the upper bounds of both darunavir/ritonavir groups never exceeded the 10 ms boundary. In the setting of this trial, darunavir/ritonavir did not appear to prolong the QTc interval.

12.3 Pharmacokinetics

Pharmacokinetics in Adults

General

Darunavir is primarily metabolized by CYP3A. Ritonavir inhibits CYP3A, thereby increasing the plasma concentrations of darunavir. When a single dose of PREZISTA 600 mg was given orally in combination with 100 mg ritonavir twice daily, 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.

The pharmacokinetics of darunavir, co-administered with low dose ritonavir (100 mg), have been evaluated in healthy adult volunteers and in HIV-1-infected subjects. Table 7 displays the population pharmacokinetic estimates of darunavir after oral administration of PREZISTA/rtv 600/100 mg twice daily [based on sparse sampling in 285 patients in study TMC114-C214 and 119 patients (integrated data) from Studies TMC114-C202 and TMC114-C213] and PREZISTA/rtv 800/100 mg once daily [based on sparse sampling in 335 patients in Study TMC114-C211] to HIV-1-infected patients.

Table 7: Population Pharmacokinetic Estimates of Darunavir at PREZISTA/rtv 800/100 mg once daily (Study TMC114-C211, 48 Week Analysis) and PREZISTA/rtv 600/100 mg twice daily (Study TMC114-C214, 48 Week Analysis and Integrated data from Studies TMC114-C213 and TMC114-C202, Primary 24-Week Analysis)			
Parameter	**Study TMC114-C211 PREZISTA/rtv 800/100 mg once daily N = 335**	**Study TMC114-C214 PREZISTA/rtv 600/100 mg twice daily N = 285**	**Studies TMC114-C213 and TMC114-C202 (integrated data) PREZISTA/rtv 600/100 mg twice daily N =119**
AUC_{24h} (ng·h/mL)*			
Mean ± Standard Deviation	93026 ± 27050	116796 ± 33594	124698 ± 32286
Median (Range)	87854 (45000-219240)	111632 (64874-355360)	123336 (67714-212980)
C_{0h} (ng/mL)			
Mean ± Standard Deviation	2282 ± 1168	3490 ± 1401	3578 ± 1151
Median (Range)	2041 (368-7242)	3307 (1517-13198)	3539 (1255-7368)
N = number of subjects with data. *AUC_{24h} is calculated as AUC_{12h}*2			

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 co-administered 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 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 twice daily 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 Dosage and Administration (2.3) and Use in Specific Populations (8.6)*].

Hepatitis B or Hepatitis C Virus Co-infection

The 48-week analysis of the data from Studies TMC114-C211 and TMC114-C214 in 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 Use in Specific Populations (8.7)*].

Gender

Population pharmacokinetic analysis showed higher mean darunavir exposure in HIV-infected females 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 Use in Specific Populations (8.5)*].

Pediatric Patients

The pharmacokinetics of darunavir in combination with ritonavir in pediatric patients has not been established. Data are insufficient at this time to recommend a dose [*see Use in Specific Populations (8.4)*].

Drug Interactions

[*See also Contraindications (4), Warnings and Precautions (5.5), and Drug Interactions (7).*]

Darunavir co-administered with ritonavir is an inhibitor of CYP3A and CYP2D6. Co-administration of darunavir and ritonavir with drugs primarily metabolized by CYP3A and CYP2D6 may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect and adverse events.

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 8 (effect of other drugs on darunavir) and Table 9 (effect of darunavir on other drugs). For information regarding clinical recommendations, *see Drug Interactions (7).*

Table 8: Drug Interactions: Pharmacokinetic Parameters for Darunavir in the Presence of Co-administered Drugs

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

N = number of subjects with data; - = no information available.
[*] q.d. = once daily
[†] b.i.d. = twice daily
[‡] The pharmacokinetic parameters of darunavir in this study were compared with the pharmacokinetic parameters following administration of darunavir/ritonavir 600/100 mg b.i.d.
[§] Ratio based on between-study comparison.
[¶] q.o.d. = every other day

Table 9: Drug Interactions: Pharmacokinetic Parameters for Co-administered Drugs in the Presence of Darunavir/Ritonavir

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

					(0.57-0.82)	(0.54-0.73)	(0.44-0.61)
Nevirapine	200 mg b.i.d.	400/100 mg b.i.d.	8	↑	1.18 (1.02-1.37)	1.27 (1.12-1.44)	1.47 (1.20-1.82)
Tenofovir Disoproxil Fumarate	300 mg q.d.	300/100 mg b.i.d.	12	↑	1.24 (1.08-1.42)	1.22 (1.10-1.35)	1.37 (1.19-1.57)
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)
Carbamazepine	200 mg b.i.d.	600/100 mg b.i.d.	16	↑	1.43 (1.34-1.53)	1.45 (1.35-1.57)	1.54 (1.41-1.68)
Carbamazepine epoxide			16	↓	0.46 (0.43-0.49)	0.46 (0.44-0.49)	0.48 (0.45-0.51)
Clarithromycin	500 mg b.i.d.	400/100 mg b.i.d.	17	↑	1.26 (1.03-1.54)	1.57 (1.35-1.84)	2.74 (2.30-3.26)
Dextromethorphan	30 mg	600/100 mg b.i.d.	12	↑	1.27 (1.58-3.25)	1.70 (1.80-4.05)	-
Dextrorphan				↓	0.86 (0.76-0.97)	0.96 (0.89-1.03)	-
Digoxin	0.4 mg	600/100 mg b.i.d.	8	↑	1.15 (0.89-1.48)	1.36 (0.81-2.27)	-
Ethinyl Estradiol (EE)	Ortho-Novum 1/35 (35 µg EE / 1 mg NE)	600/100 mg b.i.d.	11	↓	0.68 (0.61-0.74)	0.56 (0.50-0.63)	0.38 (0.27-0.54)
Norethindrone (NE)			11	↓	0.90 (0.83-0.97)	0.86 (0.75-0.98)	0.70 (0.51-0.97)
Ketoconazole	200 mg b.i.d.	400/100 mg b.i.d.	15	↑	2.11 (1.81-2.44)	3.12 (2.65-3.68)	9.68 (6.44-14.55)
R-Methadone	55-150 mg q.d.	600/100 mg b.i.d.	16	↓	0.76 (0.71-0.81)	0.84 (0.78-0.91)	0.85 (0.77-0.94)
Omeprazole	40 mg single dose	600/100 mg b.i.d.	12	↓	0.66 (0.48-0.90)	0.58 (0.50-0.66)	-

5-hydroxy omeprazole				↓	0.93 (0.71-1.21)	0.84 (0.77-0.92)	-
Paroxetine	20 mg q.d.	400/100 mg b.i.d.	16	↓	0.64 (0.59-0.71)	0.61 (0.56-0.66)	0.63 (0.55-0.73)
Pravastatin	40 mg single dose	600/100 mg b.i.d.	14	↑	1.63 (0.95-2.82)	1.81 (1.23-2.66)	-
Rifabutin	150 mg q.o.d. § when administered with PREZISTA/rtv	600/100 mg b.i.d. ¶	11	↑	0.72 (0.55-0.93)	0.93 (0.80-1.09)	1.64 (1.48-1.81)
25-*O*-desacetyl-rifabutin	300 mg q.d. when administered alone		11	↑	4.77 (4.04-5.63)	9.81 (8.09-11.9)	27.1 (22.2-33.2)
Sertraline	50 mg q.d.	400/100 mg b.i.d.	13	↓	0.56 (0.49-0.63)	0.51 (0.46-0.58)	0.51 (0.45-0.57)
Sildenafil	100 mg (single dose) administered alone 25 mg (single dose) when administered with darunavir/ ritonavir	400/100 mg b.i.d.	16	↑	0.62 (0.55-0.70)	0.97 (0.86-1.09)	-
S-warfarin	10 mg single dose	600/100 mg b.i.d.	12	↓	0.92 (0.86-0.97)	0.79 (0.73-0.85)	-
7-OH-S-warfarin			12	↑	1.42 (1.24-1.63)	1.23 (0.97-1.57)	-

N = number of subjects with data;- = no information available.
* q.d. = once daily
† b.i.d. = twice daily
‡ The pharmacokinetic parameters of lopinavir in this study were compared with the pharmacokinetic parameters following administration of lopinavir/ritonavir 400/100 mg b.i.d.
§ q.o.d. = every other day
¶ In comparison to rifabutin 300 mg q.d.

A cocktail study was conducted in 12 healthy volunteers to evaluate the effect of steady state pharmacokinetics of darunavir/ritonavir on the activity of CYP2D6 (using dextromethorphan as probe substrate), CYP2C9 (using warfarin as probe substrate), and CYP2C19 (using omeprazole as probe substrate). The pharmacokinetic results are shown in Table 9.

12.4 Microbiology

Mechanism of Action

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

Antiviral Activity

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

Resistance

Cell Culture: HIV-1 isolates with a decreased susceptibility to darunavir have been selected in cell culture and obtained from subjects treated with darunavir/ritonavir. Darunavir-resistant virus derived in cell culture from wild-type HIV had 21- to 88-fold decreased susceptibility to darunavir and developed 2 to 4 of the following amino acid substitutions S37D, R41E/T, K55Q, H69Q, K70E, T74S, V77I, or I85V in the protease. Selection in cell culture of darunavir resistant HIV-1 from nine HIV-1 strains harboring multiple PI resistance-associated mutations resulted in the overall emergence of 22 mutations in the protease gene, coding for amino acid substitutions L10F, V11I, I13V, I15V, G16E, L23I, V32I, L33F, S37N, M46I, I47V, I50V, F53L, L63P, A71V, G73S, L76V, V82I, I84V, T91A/S, and Q92R, of which L10F, V32I, L33F, S37N, M46I, I47V, I50V, L63P, A71V, and I84V were the most prevalent. These darunavir-resistant viruses had at least eight protease substitutions and exhibited 50- to 641-fold decreases in darunavir susceptibility with final EC_{50} values ranging from 125 nM to 3461 nM.

Clinical studies of darunavir/ritonavir in treatment-experienced subjects: In a pooled analysis of the 600/100 mg PREZISTA/rtv twice daily arms of Studies TMC114-C213, TMC114-C202, TMC114-C215, and the control arms of etravirine studies TMC125-C206 and TMC125-C216, the amino acid substitutions V32I and I54L or M developed most frequently on PREZISTA/rtv in 41% and 25%, respectively, of the treatment-experienced subjects who experienced virologic failure, either by rebound or by never being suppressed (< 50 copies/mL). Other substitutions that developed frequently in PREZISTA/rtv virologic failure isolates occurred at amino acid positions V11I, I15V, L33F, I47V, I50V, and L89V. These amino acid substitutions were associated with decreased susceptibility to darunavir; 90% of the virologic failure isolates had a > 7-fold decrease in susceptibility to darunavir at failure. The median darunavir phenotype (fold change from reference) of the virologic failure isolates was 4.3-fold at baseline and 85-fold at failure. Amino acid substitutions were also observed in the protease cleavage sites in the Gag polyprotein of some PREZISTA/rtv virologic failure isolates.

In the 48-week analysis of the Phase 3 Study TMC114-C214, the number of virologic failures was 17% (52/298) in the group of subjects receiving PREZISTA/rtv 600/100 mg twice daily compared to 28% (84/297) of subjects receiving lopinavir/ritonavir 400/100 mg twice daily. Examination of subjects who failed on PREZISTA/rtv 600/100 mg twice daily and had post-baseline genotypes and phenotypes showed that 6 subjects (6/33; 18%) developed PI substitutions on darunavir/ritonavir treatment resulting in decreased susceptibility to darunavir. The most common emerging PI substitutions in these virologic failures were V32I, I47V, I54L, T74P and L76V. These amino acid substitutions were associated with 44- to 607-fold decreased susceptibility to darunavir at failure. Five of the 6 had baseline PI resistance-associated substitutions and baseline darunavir phenotypes > 7. In the comparator arm, 28 (28/69; 41%) lopinavir/ritonavir virologic failures had reduced susceptibility to lopinavir (> 10-fold change) at failure. Of those 28 lopinavir/ritonavir failures, 13 had reduced susceptibility to lopinavir at baseline. The other 15 lopinavir/ritonavir virologic failures developed substitutions on lopinavir treatment resulting in decreased lopinavir susceptibility. The most common substitutions developing were L10I/F, I47V/A, L76V, M46I/L and I54V.

Clinical studies of darunavir/ritonavir in treatment-naive subjects: In the 48-week analysis of the Phase 3 Study TMC114-C211, the number of virologic failures was 10% in the group of subjects receiving PREZISTA/rtv 800/100 mg once daily compared to 14% of subjects receiving lopinavir/ritonavir 800/200 mg per day. No emergent PI-resistance associated substitutions were identified in the virologic failures with post-baseline genotypic data (n=12) in the PREZISTA/rtv arm and none of the darunavir virologic failures had a decrease in darunavir susceptibility at failure. None of the lopinavir/ritonavir virologic failures had resistance to lopinavir at failure. The M184V substitution and resistance to emtricitabine, which was included in the fixed background regimen, was identified in 1 virologic failure of the PREZISTA/rtv arm and 2 virologic failures in the lopinavir/ritonavir arm.

Cross-resistance

Cross-resistance among PIs has been observed. Darunavir has a < 10-fold decreased susceptibility in cell culture against 90% of 3309 clinical isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and/or tipranavir showing that viruses resistant to these PIs remain susceptible to darunavir.

Darunavir-resistant viruses were not susceptible to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir or saquinavir in cell culture. However, six of nine darunavir-resistant viruses selected in cell culture from PI-resistant viruses showed a fold change in EC_{50} values < 3 for tipranavir, indicative of limited cross-resistance between darunavir and tipranavir. In Studies TMC114-C213, TMC114-C202, and TMC114-C215, 34% (64/187) of subjects in the darunavir/ritonavir arm whose baseline isolates had decreased susceptibility to tipranavir (tipranavir fold change > 3) achieved < 50 copies/mL serum HIV RNA levels at Week 96. Of the viruses isolated from subjects experiencing virologic failure on PREZISTA/rtv 600/100 mg twice daily (> 7 fold change), 41% were still susceptible to tipranavir and 10% were susceptible to saquinavir while less than 2% were susceptible to the other protease inhibitors (amprenavir, atazanavir, indinavir, lopinavir or nelfinavir).

In Study TMC114-C214, 18% (6/33) of the darunavir/ritonavir virologic failures were resistant to the approved PIs amprenavir, atazanavir, lopinavir, and nelfinavir and 15% (5/33) were resistant to indinavir, saquinavir and tipranavir. Most of the virologic failures (83%; 5/6) were resistant to the PIs at baseline.

Cross-resistance between darunavir and nucleoside/nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, fusion inhibitors, CCR5 co-receptor antagonists, or integrase inhibitors is unlikely because the viral targets are different.

Baseline Genotype/Phenotype and Virologic Outcome Analyses

Genotypic and/or phenotypic analysis of baseline virus may aid in determining darunavir susceptibility before initiation of PREZISTA/rtv 600/100 mg twice daily therapy. The effect of baseline genotype and phenotype on virologic response at 96 weeks was analyzed in as-treated analyses using pooled data from the Phase 2b studies (Studies TMC114-C213, TMC114-C202, and TMC114-C215) (n=439). The findings were confirmed with additional genotypic and phenotypic data from the control arms of etravirine Studies TMC125-C206 and TMC125-C216 at Week 24 (n=591).

Diminished virologic responses were observed in subjects with 5 or more baseline IAS-defined primary protease inhibitor resistance-associated substitutions (D30N, V32I, L33F, M46I/L, I47A/V, G48V, I50L/V, I54L/M, L76V, V82A/F/L/S/T, I84V, N88S, L90M) (see Table 10).

Table 10: Response to PREZISTA/rtv 600/100 mg twice daily by Baseline Number of IAS-Defined Primary PI Resistance-Associated Substitutions: As-treated Analysis of Studies TMC114-C213, TMC114-C202, and TMC114-C215

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

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

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

Baseline darunavir phenotype (shift in susceptibility relative to reference) was shown to be a predictive factor of virologic outcome. Response rates assessed by baseline darunavir phenotype are shown in Table 11. These baseline phenotype groups are based on the select patient populations in the Studies TMC114-C213, TMC114-C202, and TMC114-C215, and are not meant to represent definitive clinical susceptibility breakpoints for PREZISTA/rtv. The data are provided to give clinicians information on the likelihood of virologic success based on pre-treatment susceptibility to darunavir.

Table 11: Response (HIV-1 RNA < 50 copies/mL at Week 96) to PREZISTA/rtv 600/100 mg twice daily by Baseline Darunavir Phenotype and by Use of Enfuvirtide (ENF): As-treated Analysis of Studies TMC114-C213, TMC114-C202, and TMC114-C215

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis and Mutagenesis

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

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

Impairment of Fertility

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

13.2 Animal Toxicology and/or Pharmacology

In juvenile rats single doses of darunavir (20 mg/kg to 160 mg/kg at ages 5-11 days) or multiple doses of darunavir (40 mg/kg to 1000 mg/kg at age 12 days) caused mortality. The mortalities were associated with convulsions in some of the animals. Within this age range exposures in plasma, liver and brain were dose and age dependent and were considerably greater than those observed in adult rats. These findings were attributed to the ontogeny of the CYP450 liver enzymes involved in the metabolism of darunavir and the immaturity of the blood-brain barrier. No treatment-related mortalities were noted in juvenile rats after a single dose of darunavir at 1000 mg/kg on day 26 of age or after repeat dosing at 500 mg/kg from day 23 to 50 of age. The exposures and toxicity profile in the older animals (day 23 or day 26) were comparable to those observed in adult rats. In humans, the activity of drug-metabolizing enzymes approaches adult values by 3 years of age.

14 CLINICAL STUDIES

14.1 Description of Clinical Studies

The evidence of efficacy of PREZISTA/rtv is based on the analyses of 48-week data from 2 randomized, controlled open-label Phase 3 trials in treatment-naïve (TMC114-C211) and antiretroviral treatment-experienced (TMC114-C214) HIV-1-infected adult subjects. In addition, 96-week data is included from 2 randomized, controlled Phase 2b trials, TMC114-C213 and TMC114-C202, in antiretroviral treatment-experienced HIV-1-infected adult subjects.

14.2 Antiretroviral Treatment-Naïve Adult Subjects

Study TMC114-C211

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

HIV-1-infected subjects who were eligible for this trial had plasma HIV-1 RNA ≥ 5000 copies/mL. Randomization was stratified by screening plasma viral load (HIV-1 RNA < 100,000 copies/mL or ≥ 100,000 copies/mL) and screening CD4+ cell count (< 200 cells/mm^3 or ≥ 200 cells/mm^3). Virologic response was defined as a confirmed plasma HIV-1 RNA viral load < 50 copies/mL. Analyses included 689 subjects in Study TMC114-C211 who had completed 48 weeks of treatment or discontinued earlier.

Demographics and baseline characteristics were balanced between the PREZISTA/rtv arm and the lopinavir/ritonavir arm (see Table 12). Table 12 compares the demographic and baseline characteristics between subjects in the PREZISTA/rtv 800/100 mg once daily arm and subjects in the lopinavir/ritonavir 800/200 mg per day arm in Study TMC114-C211.

Table 12: Demographic and Baseline Characteristics of Subjects in Study TMC114-C211

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

Week 48 outcomes for subjects on PREZISTA/rtv 800/100 mg once daily from Study TMC114-C211 are shown in Table 13.

Table 13: Outcomes of Randomized Treatment Through Week 48 of Study TMC114-C211

	Randomized Study TMC114-C211	
	PREZISTA/rtv 800/100 mg once daily + TDF/FTC N = 343	**lopinavir/ritonavir 800/200 mg per day + TDF/FTC N = 346**
Virologic Responders HIV-1 RNA < 50 copies/mL	84%	78%
Virologic failures	6%	10%
Rebounder*	2%	3%
Never suppressed†	4%	8%
Death or discontinuation due to adverse events	4%	6%
Discontinuation due to other reasons	7%	6%

N = total number of subjects with data
*Subjects with a confirmed viral load < 50 copies/mL before Week 48, but without a confirmed viral load < 50 copies/mL at Week 48
† Subjects who never reached a confirmed viral load < 50 copies/mL before Week 48

In Study TMC114-C211 through 48 weeks of treatment, the proportion of subjects with HIV-1 RNA < 400 copies/mL in the arm receiving PREZISTA/rtv 800/100 mg once daily compared to the arm receiving lopinavir/ritonavir 800/200 mg per day was 87.8% and 85.3%, respectively. The median increase from baseline in CD4+ cell counts was comparable for both treatment groups (137 cells/mm^3 and 141 cells/mm^3 in the PREZISTA/rtv 800/100 mg once daily arm and the lopinavir/ritonavir 800/200 mg per day arm, respectively).

The virological response (< 50 copies/mL) by baseline viral load is presented in Table 14.

Table 14: Virological Response (< 50 copies/mL) by BaselineViral Load

	PREZISTA/rtv 800/100 mg once daily n=343		**lopinavir/ritonavir 800/200 mg per day n=346**		**Treatment Difference**
	N	**number of responders n (%)**	**N**	**number of responders n (%)**	**Difference in % response (95% CI of difference in % response)**
Baseline plasma viral load (copies/mL)					
< 100,000	226	194 (86)	226	191 (85)	1.3 (-5; 8)
≥ 100,000	117	93 (80)	120	80 (67)	12.8 (2; 24)

14.3 Antiretroviral Treatment-Experienced Adult Subjects

Study TMC114-C214

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

HIV-1-infected subjects who were eligible for this trial had plasma HIV-1 RNA > 1000 copies/mL and were on a highly active antiretroviral therapy regimen (HAART) for at least 12 weeks. Virologic response was defined as a confirmed plasma HIV-1 RNA viral load < 400 copies/mL. Analyses included 595 subjects in Study TMC114-C214 who had completed 48 weeks of treatment or discontinued earlier.

Demographics and baseline characteristics were balanced between the PREZISTA/rtv arm and the lopinavir/ritonavir arm (see Table 15). Table 15 compares the demographic and baseline characteristics between subjects in the PREZISTA/rtv 600/100 mg twice daily arm and subjects in the lopinavir/ritonavir 400/100 mg twice daily arm in Study TMC114-C214.

Table 15: Demographic and Baseline Characteristics of Subjects in Study TMC114-C214

	Randomized Study TMC114-C214	
	PREZISTA/rtv 600/100 mg twice daily + OBR N = 298	**lopinavir/ritonavir 400/100 mg twice daily + OBR N = 297**
Demographic Characteristics		
Median Age (years) (range, years)	40 (18-68)	41 (22-76)
Sex		
Male	77%	81%
Female	23%	19%
Race		
White	54%	57%
Black	18%	17%
Hispanic	15%	15%
Asian	9%	9%
Baseline Characteristics		
Mean Baseline Plasma HIV-1 RNA (log_{10} copies/mL)	4.33	4.28
Median Baseline CD4+ Cell Count (cells/mm^3) (range, cells/mm^3)	235 (3-831)	230 (2-1096)
Percentage of Patients with Baseline Viral Load ≥ 100,000 copies/mL	19%	17%
Percentage of Patients with Baseline CD4+ Cell Count < 200 cells/mm^3	40%	40%
Median Darunavir Fold Change (range)	0.60 (0.10-37.40)	0.60 (0.1-43.8)
Median Lopinavir Fold Change (range)	0.70 (0.40-74.40)	0.80 (0.30-74.50)
Median Number of Resistance-Associated*:		
PI mutations	4	4
NNRTI mutations	1	1
NRTI mutations	2	2
Percentage of Subjects with Number of		

Baseline Primary Protease Inhibitor Mutations*: ≤ 1 2 ≥ 3	 78% 8% 13%	 80% 9% 11%
Median Number of ARVs Previously Used†: NRTIs NNRTIs PIs (excluding low-dose ritonavir)	 4 1 1	 4 1 1
Percentage of Subjects Resistant‡ to All Available§ PIs at Baseline, excluding Darunavir	2%	3%

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

Week 48 outcomes for subjects on PREZISTA/rtv 600/100 mg twice daily from Study TMC114-C214 are shown in Table 16.

Table 16: Outcomes of Randomized Treatment Through Week 48 of Study TMC114-C214

	Randomized Study TMC114-C214	
	PREZISTA/rtv 600/100 mg twice daily + OBR N = 298	**lopinavir/ritonavir 400/100 mg twice daily + OBR N = 297**
Virologic Responders HIV-1 RNA < 400 copies/mL (HIV-1 RNA < 50 copies/mL)	 77% (71%)	 67% (60%)
Virologic failures	11%	21%
Lack of initial response*	7%	14%
Rebounder†	3%	7%
Discontinued due to virologic failure: never suppressed‡	0%	< 1%
Death or discontinuation due to adverse events	6%	5%
Discontinuation due to other reasons	7%	9%

N = total number of subjects with data
* Subjects with viral load ≥ 400 copies/mL at Week 16
† Subjects with a confirmed viral load < 400 copies/mL before Week 48, but without a confirmed viral load < 400 copies/mL at Week 48
‡ Subjects who never reached a confirmed viral load < 400 copies/mL before Week 48

In Study TMC114-C214 through 48 weeks of treatment, the median increase from baseline in CD4+ cell counts was comparable for both treatment groups (88 cells/mm^3 and 81 cells/mm^3 in the PREZISTA/rtv 600/100 mg twice daily arm and lopinavir/ritonavir 400/100 mg twice daily arm, respectively).

Studies TMC114-C213 and TMC114-C202

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

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

The virologic response rate was evaluated in subjects receiving PREZISTA/rtv plus an OBR versus a control group receiving an investigator-selected PI(s) regimen plus an OBR. Prior to randomization, PI(s) and OBR were selected by the investigator based on genotypic resistance testing and prior ARV history. The OBR consisted of at least 2 NRTIs with or without enfuvirtide. Selected PI(s) in the control arm included: lopinavir in 36%, (fos)amprenavir in 34%, saquinavir in 35% and atazanavir in 17%; 98% of control subjects received a ritonavir boosted PI regimen out of which 23% of control subjects used dual-boosted PIs. Approximately 47% of all subjects used enfuvirtide, and 35% of the use was in subjects who were ENF-naïve. Virologic response was defined as a decrease in plasma HIV-1 RNA viral load of at least 1.0 $\log_{10}$ 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 (see Table 17). Table 17 compares the demographic and baseline characteristics between subjects in the PREZISTA/rtv 600/100 mg twice daily arm and subjects in the comparator PI arm in the pooled analysis of Studies TMC114-C213 and TMC114-C202.

Table 17: Demographic and 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 twice daily + OBR N = 131	**Comparator PI(s) + OBR N = 124**
Demographic Characteristics		
Median Age (years) (range, years)	43 (27-73)	44 (25-65)
Sex		
Male	89%	88%
Female	11%	12%
Race		
White	81%	73%
Black	10%	15%
Hispanic	7%	8%
Baseline Characteristics		
Mean Baseline Plasma HIV-1 RNA ($\log_{10}$ copies/mL)	4.61	4.49
Median Baseline CD4+ Cell Count (cells/mm^3) (range, cells/mm^3)	153 (3-776)	163 (3-1274)
Percentage of Patients with Baseline Viral	24%	29%

Load > 100,000 copies/mL		
Percentage of Patients with Baseline CD4+ Cell Count < 200 cells/mm^3	67%	58%
Median Darunavir Fold Change	4.3	3.3
Median Number of Resistance-Associated*:		
PI mutations	12	12
NNRTI mutations	1	1
NRTI mutations	5	5
Percentage of Subjects with Number of Baseline Primary Protease Inhibitor Mutations*:		
≤ 1	8%	9%
2	22%	21%
≥ 3	70%	70%
Median Number of ARVs Previously Used†:		
NRTIs	6	6
NNRTIs	1	1
PIs (excluding low-dose ritonavir)	5	5
Percentage of Subjects Resistant† to All Available‡ PIs at Baseline, excluding Tipranavir and Darunavir	63%	61%
Percentage of Subjects with Prior Use of Enfuvirtide	20%	17%

* Johnson VA, Brun-Vezinet F, Clotet B, et al. Update of the drug resistance mutations in HIV-1: Fall 2006. Top HIV Med 2006; 14(3): 125-130

† Based on phenotype (Antivirogram™)

‡ Commercially available PIs at the time of study enrollment

Week 96 outcomes for subjects on the recommended dose PREZISTA/rtv 600/100 mg twice daily from the pooled Studies TMC114-C213 and TMC114-C202 are shown in Table 18.

Table 18: Outcomes of Randomized Treatment Through Week 96 of the Studies TMC114-C213 and TMC114-C202 (Pooled Analysis)

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

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

PREZISTA tablets are packaged in bottles in the following configuration:
300 mg tablets—bottles of 120 (NDC 59676-560-01)
400 mg tablets—bottles of 60 (NDC 59676-561-01)
600 mg tablets—bottles of 60 (NDC 59676-562-01)

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

17 PATIENT COUNSELING INFORMATION

[See FDA-Approved Patient Labeling (17.5)]

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

17.1 General

Patients should be informed that PREZISTA is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. 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.

17.2 Instructions for Use

General

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.

Patients Taking 800 mg of PREZISTA Once Daily

If a patient misses a dose of PREZISTA (two 400 mg tablets) or ritonavir (NORVIR®) by more than 12 hours, the patient should be told to wait and then take the next dose of PREZISTA (two 400 mg tablets) and ritonavir (NORVIR®) at the regularly scheduled time. If the patient misses a dose of PREZISTA (two 400 mg tablets) or ritonavir (NORVIR®) by less than 12 hours, the patient should be told to take PREZISTA (two 400 mg tablets) and ritonavir (NORVIR®) immediately, and then take the next dose of PREZISTA (two 400 mg tablets) and ritonavir (NORVIR®) at the regularly scheduled time. If a dose of PREZISTA (two 400 mg tablets) 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 (two 400 mg tablets) or ritonavir (NORVIR®) at any one time.

Patients Taking 600 mg of PREZISTA Twice Daily

If a patient misses a dose of PREZISTA (one 600 mg tablet or two 300 mg tablets) or ritonavir (NORVIR®) by more than 6 hours, the patient should be told to wait and then take the next dose of PREZISTA (one 600 mg tablet or two 300 mg tablets) and ritonavir (NORVIR®) at the regularly scheduled time. If the patient misses a dose of PREZISTA (one 600 mg tablet or two 300 mg tablets) or ritonavir (NORVIR®) by less than 6 hours, the patient should be told to take PREZISTA (one 600 mg tablet or two 300 mg tablets) and ritonavir (NORVIR®) immediately, and then take the next dose of PREZISTA (one 600 mg tablet or two 300 mg tablets) and ritonavir (NORVIR®) at the regularly scheduled time. If a dose of PREZISTA (one 600 mg tablet or two 300 mg tablets) 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 (one 600 mg tablet or two 300 mg tablets) or ritonavir (NORVIR®) at any one time.

17.3 Drug Interactions

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.

17.4 Fat Redistribution

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.

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

10101706

17.5 FDA-Approved Patient Labeling

PREZISTA® (darunavir) Tablets

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

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

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

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

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

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

WHAT IS PREZISTA?

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

HOW DOES PREZISTA WORK?

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

PREZISTA is always taken with and at the same time as 100 mg of ritonavir (NORVIR®), in combination with other anti-HIV medicines. PREZISTA should also be taken with food.

DOES PREZISTA CURE HIV OR AIDS?

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

DOES PREZISTA REDUCE THE RISK OF PASSING HIV TO OTHERS?

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

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

WHAT SHOULD I TELL MY DOCTOR BEFORE I TAKE PREZISTA?

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

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

WHO SHOULD NOT TAKE PREZISTA?**

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

Do not take 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:

Type of Drug	Examples of Generic Names (Brand Names)
Ergot Derivatives (to treat migraine and headaches)	dihydroergotamine (D.H.E. 45®, Migranal®) ergonovine ergotamine (Cafergot®, Ergomar®) methylergonovine
Gastrointestinal Motility Agent (to treat some digestive conditions)	cisapride

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

CAN PREZISTA BE TAKEN WITH OTHER MEDICATIONS?**

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

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

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

Type of Drug	Examples of Generic Names (Brand Names)
Antiarrhythmics (to treat abnormal heart rhythms)	bepridil lidocaine (Lidoderm®) quinidine amiodarone (Cordarone®) digoxin (Lanoxin®) flecainide (Tambocor®) propafenone (Rythmol®)
Anticoagulants (to treat and prevent blood clots)	warfarin (Coumadin®)
Anticonvulsants (to treat epilepsy and prevent seizures)	carbamazepine (Tegretol®, Carbatrol®) phenobarbital phenytoin (Dilantin®, Phenytek®)
Antidepressants (to treat depression)	trazodone (Desyrel®) desipramine (Norpramin®)
Anti-infectives (to treat bacterial infections)	clarithromycin (Biaxin®)

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

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

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

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

HOW SHOULD I TAKE PREZISTA?

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

- For adults who have never taken anti-HIV medicines, the usual dose is 800 mg (two 400 mg tablets) of PREZISTA, together with 100 mg (one 100 mg capsule) of ritonavir (NORVIR®), once daily *every day*.
- For adults who have taken anti-HIV medicines in the past, the usual dose is 600 mg (one 600 mg tablet or two 300 mg tablets) of PREZISTA, together with 100 mg (one 100 mg capsule) of ritonavir (NORVIR®), twice daily *every day*.

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

Take PREZISTA and ritonavir (NORVIR®) **with food.** 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.

Patients taking 800 mg of PREZISTA once daily

If you miss a dose of PREZISTA (two 400 mg tablets) or ritonavir (NORVIR®) by more than 12 hours, wait and then take the next dose of PREZISTA (two 400 mg tablets) and ritonavir (NORVIR®) at the regularly scheduled time. If you miss a dose of PREZISTA (two 400 mg tablets) or ritonavir (NORVIR®) by less than 12 hours, take your missed dose of PREZISTA (two 400 mg tablets) and ritonavir (NORVIR®) immediately. Then take your next dose of PREZISTA (two 400 mg tablets) and ritonavir (NORVIR®) at the regularly scheduled time.

Patients taking 600 mg of PREZISTA twice daily

If you miss a dose of PREZISTA (one 600 mg tablet or two 300 mg tablets) or ritonavir (NORVIR®) by more than 6 hours, wait and then take the next dose of PREZISTA (one 600 mg tablet or two 300 mg tablets) and ritonavir (NORVIR®) at the regularly scheduled time. If you miss a dose of PREZISTA (one 600 mg tablet or two 300 mg tablets) or ritonavir (NORVIR®) by less than 6 hours, take your missed dose of PREZISTA (one 600 mg tablet or two 300 mg tablets) and ritonavir (NORVIR®) immediately. Then take your next dose of PREZISTA (one 600 mg tablet or two 300 mg tablets) and ritonavir (NORVIR®) at the regularly scheduled time.

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

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

WHAT ARE THE POSSIBLE SIDE EFFECTS OF PREZISTA?

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

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

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

Rash has been reported in 10.3% of 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.

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

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

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

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

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

WHAT DO PREZISTA TABLETS LOOK LIKE?

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

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

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

HOW SHOULD I STORE PREZISTA TABLETS?

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

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

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

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

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

 Revised: October 2008

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