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) oral suspension
PREZISTA® (darunavir) tablet, for oral use
Initial U.S. Approval: 2006

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

Contraindications (4) 4/2022

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

PREZISTA is a human immunodeficiency virus (HIV-1) protease inhibitor indicated for the treatment of HIV-1 infection in adult and pediatric patients 3 years of age and older. PREZISTA must be co-administered with ritonavir (PREZISTA/ritonavir) and with other antiretroviral agents. (1)

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

- Testing:
  - In treatment-experienced patients, treatment history genotypic and/or phenotypic testing is recommended prior to initiation of therapy with PREZISTA/ritonavir to assess drug susceptibility of the HIV-1 virus (2.1, 12.4)
  - Monitor serum liver chemistry tests before and during therapy with PREZISTA/ritonavir. (2.1, 2.2, 5.2)
- Treatment-naïve adult patients and treatment-experienced adult patients with no darunavir resistance associated substitutions: 800 mg (one 800 mg tablet) taken with ritonavir 100 mg once daily and with food. (2.3)
- Treatment-experienced adult patients with at least one darunavir resistance associated substitution: 600 mg (one 600 mg tablet) taken with ritonavir 100 mg twice daily and with food. (2.3)
- Pregnant patients: 600 mg (one 600 mg tablet) taken with ritonavir 100 mg twice daily and with food. (2.4)
- Pediatric patients (3 to less than 18 years of age and weighing at least 10 kg): dosage of PREZISTA and ritonavir is based on body weight and should not exceed the adult dose. PREZISTA should be taken with ritonavir and with food. (2.5)
- PREZISTA/ritonavir is not recommended for use in patients with severe hepatic impairment. (2.6)

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

- Oral suspension: 100 mg per mL (3)
- Tablets: 75 mg, 150 mg, 600 mg, and 800 mg (3)

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

- Co-administration of PREZISTA/ritonavir 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). (4)

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

- Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported with PREZISTA/ritonavir. 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. Post-marketing cases of liver injury, including some fatalities, have been reported. (5.2)
- Skin reactions ranging from mild to severe, including Stevens-Johnson Syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms and acute generalized exanthematous pustulosis, have been reported. Discontinue treatment if severe reaction develops. (5.3)
- 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 or immune reconstitution syndrome. (5.7, 5.8)
- Patients with hemophilia may develop increased bleeding events. (5.9)
- PREZISTA/ritonavir is not recommended in pediatric patients below 3 years of age in view of toxicity and mortality observed in juvenile rats dosed with darunavir up to days 23 to 26 of age. (5.10)

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

- The most common clinical adverse drug reactions to PREZISTA/ritonavir (incidence greater than or equal to 5%) of at least moderate intensity (greater than or equal to Grade 2) were diarrhea, nausea, rash, headache, abdominal pain and vomiting. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Products, LP at 1-800-JANSSEN (1-800-526-7736) 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 concentrations of other drugs and other drugs may alter the concentrations of darunavir. The potential drug-drug interactions must be considered prior to and during therapy. (4, 5.5, 7, 12.3)

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

- Pregnancy: Total darunavir exposures were generally lower during pregnancy compared to postpartum period. The reduction in darunavir exposures during pregnancy were greater for once daily dosing compared to the twice daily dosing regimen. (8.1, 12.3)
- Lactation: Women infected with HIV should be instructed not to breastfeed due to the potential for HIV transmission. (8.2)
- Pediatrics: Not recommended for patients less than 3 years of age. (8.4)

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

Revised: 10/2022

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 ritonavir (PREZISTA/ritonavir), in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV-1) infection in adult and pediatric patients 3 years of age and older *[see Use in Specific Populations (8.4) and Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Testing Prior to Initiation of PREZISTA/ritonavir

In treatment-experienced patients, treatment history, genotypic and/or phenotypic testing is recommended to assess drug susceptibility of the HIV-1 virus *[see Microbiology (12.4)]*. Refer to *Dosage and Administration (2.3), (2.4) and (2.5)* for dosing recommendations.

Appropriate laboratory testing such as serum liver biochemistries should be conducted prior to initiating therapy with PREZISTA/ritonavir *[see Warnings and Precautions (5.2)]*.

2.2 Monitoring During Treatment with PREZISTA/ritonavir

Patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases should be monitored for elevation in serum liver biochemistries, especially during the first several months of PREZISTA/ritonavir treatment *[see Warnings and Precautions (5.2)]*.

2.3 Recommended Dosage in Adult Patients

PREZISTA must be co-administered with ritonavir to exert its therapeutic effect. Failure to correctly co-administer PREZISTA with ritonavir will result in plasma levels of darunavir that will be insufficient to achieve the desired antiviral effect and will alter some drug interactions.

Patients who have difficulty swallowing PREZISTA tablets can use the 100 mg per mL PREZISTA oral suspension.

Treatment-Naïve Adult Patients

The recommended oral dose of PREZISTA is 800 mg (one 800 mg tablet or 8 mL of the oral suspension) taken with ritonavir 100 mg (one 100 mg tablet or capsule or 1.25 mL of a 80 mg per mL ritonavir oral solution) once daily and with food. An 8 mL PREZISTA dose should be taken as two 4 mL administrations with the included oral dosing syringe.

Treatment-Experienced Adult Patients

The recommended oral dosage for treatment-experienced adult patients is summarized in Table 1.

Baseline genotypic testing is recommended for dose selection. However, when genotypic testing is not feasible, PREZISTA 600 mg taken with ritonavir 100 mg twice daily is recommended.

Table 1: Recommended PREZISTA/ritonavir Dosage in Treatment-Experienced Adult Patients

Baseline Resistance	Formulation and Recommended Dosing	
	PREZISTA tablets with ritonavir tablets or capsule	**PREZISTA oral suspension (100 mg/mL) with ritonavir oral solution (80 mg/mL)**
With no darunavir resistance associated substitutions[a]	One 800 mg PREZISTA tablet with one 100 mg ritonavir tablet/capsule, taken once daily with food	8 mL[b] PREZISTA oral suspension with 1.25 mL ritonavir oral solution, taken once daily with food
With at least one darunavir resistance associated substitutions[a], or with no baseline resistance information	One 600 mg PREZISTA tablet with one 100 mg ritonavir tablet/capsule, taken twice daily with food	6 mL PREZISTA oral suspension with 1.25 mL ritonavir oral solution, taken twice daily with food

[a] V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V and L89V

[b] An 8 mL darunavir dose should be taken as two 4 mL administrations with the included oral dosing syringe.

2.4 Recommended Dosage During Pregnancy

The recommended dosage in pregnant patients is PREZISTA 600 mg taken with ritonavir 100 mg twice daily with food.

PREZISTA 800 mg taken with ritonavir 100 mg once daily should only be considered in certain pregnant patients who are already on a stable PREZISTA 800 mg with ritonavir 100 mg once daily regimen prior to pregnancy, are virologically suppressed (HIV-1 RNA less than 50 copies per mL), and in whom a change to twice daily PREZISTA 600 mg with ritonavir 100 mg may compromise tolerability or compliance.

2.5 Recommended Dosage in Pediatric Patients (age 3 to less than 18 years)

Healthcare professionals should pay special attention to accurate dose selection of PREZISTA, transcription of the medication order, dispensing information and dosing instruction to minimize risk for medication errors, overdose, and underdose.

Prescribers should select the appropriate dose of PREZISTA/ritonavir for each individual child based on body weight (kg) and should not exceed the recommended dose for adults.

Before prescribing PREZISTA, children weighing greater than or equal to 15 kg should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow a tablet, the use of PREZISTA oral suspension should be considered.

The recommended dose of PREZISTA/ritonavir for pediatric patients (3 to less than 18 years of age and weighing at least 10 kg is based on body weight (see Tables 2, 3, 4, and 5) and should not exceed the recommended adult dose. PREZISTA should be taken with ritonavir and with food.

The recommendations for the PREZISTA/ritonavir dosage regimens were based on pediatric clinical trial data and population pharmacokinetic modeling and simulation *[see Use in Specific Populations (8.4) and Clinical Pharmacology (12.3)]*.

Dosing Recommendations for Treatment-Naïve Pediatric Patients or Antiretroviral Treatment-Experienced Pediatric Patients with No Darunavir Resistance Associated Substitutions

Pediatric Patients Weighing At Least 10 kg but Less than 15 kg

The weight-based dose in antiretroviral treatment-naïve pediatric patients or antiretroviral treatment-experienced pediatric patients with no darunavir resistance associated substitutions is PREZISTA 35 mg/kg once daily with ritonavir 7 mg/kg once daily using the following table:

Table 2: Recommended Dose for Pediatric Patients Weighing 10 kg to Less Than 15 kg Who are Treatment-Naïve or Treatment-Experienced with No Darunavir Resistance Associated Substitutions[a]

	Formulation: PREZISTA oral suspension (100 mg/mL) and ritonavir oral solution (80 mg/mL)
Body weight (kg)	**Dose: once daily with food**
Greater than or equal to 10 kg to less than 11 kg	PREZISTA 3.6 mL[b] (350 mg) with ritonavir 0.8 mL (64 mg)
Greater than or equal to 11 kg to less than 12 kg	PREZISTA 4 mL[b] (385 mg) with ritonavir 0.8 mL (64 mg)
Greater than or equal to 12 kg to less than 13 kg	PREZISTA 4.2 mL (420 mg) with ritonavir 1 mL (80 mg)
Greater than or equal to 13 kg to less than 14 kg	PREZISTA 4.6 mL[b] (455 mg) with ritonavir 1 mL (80 mg)
Greater than or equal to 14 kg to less than 15 kg	PREZISTA 5 mL[b] (490 mg) with ritonavir 1.2 mL (96 mg)

[a] darunavir resistance associated substitutions: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

[b] The 350 mg, 385 mg, 455 mg and 490 mg darunavir dose for the specified weight groups were rounded up for suspension dosing convenience to 3.6 mL, 4 mL, 4.6 mL and 5 mL, respectively.

Pediatric Patients Weighing At Least 15 kg

Pediatric patients weighing at least 15 kg can be dosed with PREZISTA oral tablet(s) or suspension using the following table:

Table 3: Recommended Dose for Pediatric Patients Weighing At Least 15 kg Who are Treatment-Naïve or Treatment-Experienced with No Darunavir Resistance Associated Substitutions[a]

	Formulation: PREZISTA tablet(s) and ritonavir capsules or tablets (100 mg)	**Formulation: PREZISTA oral suspension (100 mg/mL) and ritonavir oral solution (80 mg/mL)**
Body weight (kg)	**Dose: once daily with food**	**Dose: once daily with food**
Greater than or equal to 15 kg to less than 30 kg	PREZISTA 600 mg with ritonavir 100 mg	PREZISTA 6 mL (600 mg) with ritonavir 1.25 mL (100 mg)
Greater than or equal to 30 kg to less than 40 kg	PREZISTA 675 mg with ritonavir 100 mg	PREZISTA 6.8 mL[bc] (675 mg) with ritonavir 1.25 mL (100 mg)
Greater than or equal to 40 kg	PREZISTA 800 mg with ritonavir 100 mg	PREZISTA 8 mL[c] (800 mg) with ritonavir 1.25 mL (100 mg)

[a] darunavir resistance associated substitutions: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

[b] The 675 mg dose using darunavir tablets for this weight group is rounded up to 6.8 mL for suspension dosing convenience.

[c] The 6.8 mL and 8 mL darunavir dose should be taken as two (3.4 mL or 4 mL respectively) administrations with the included oral dosing syringe.

Dosing Recommendations for Treatment-Experienced Pediatric Patients with At Least One Darunavir Resistance Associated Substitutions

Pediatric Patients Weighing At Least 10 kg but Less than 15 kg

The weight-based dose in antiretroviral treatment-experienced pediatric patients with at least one darunavir resistance associated substitution is PREZISTA 20 mg/kg twice daily with ritonavir 3 mg/kg twice daily using the following table:

Table 4: Recommended Dose for Pediatric Patients Weighing 10 kg to Less Than 15 kg Who are Treatment-Experienced with At Least One Darunavir Resistance Associated Substitution[a]

	Formulation: PREZISTA oral suspension (100 mg/mL) and ritonavir oral solution (80 mg/mL)
Body weight (kg)	**Dose: twice daily with food**
Greater than or equal to 10 kg to less than 11 kg	PREZISTA 2 mL (200 mg) with ritonavir 0.4 mL (32 mg)
Greater than or equal to 11 kg to less than 12 kg	PREZISTA 2.2 mL (220 mg) with ritonavir 0.4 mL (32 mg)
Greater than or equal to 12 kg to less than 13 kg	PREZISTA 2.4 mL (240 mg) with ritonavir 0.5 mL (40 mg)
Greater than or equal to 13 kg to less than 14 kg	PREZISTA 2.6 mL (260 mg) with ritonavir 0.5 mL (40 mg)
Greater than or equal to 14 kg to less than 15 kg	PREZISTA 2.8 mL (280 mg) with ritonavir 0.6 mL (48 mg)

[a] darunavir resistance associated substitutions: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

Pediatric Patients Weighing At Least 15 kg

Pediatric patients weighing at least 15 kg can be dosed with PREZISTA oral tablet(s) or suspension using the following table:

Table 5: Recommended Dose for Pediatric Patients Weighing At Least 15 kg Who are Treatment-Experienced with At Least One Darunavir Resistance Associated Substitution[a]

	Formulation: PREZISTA tablet(s) and ritonavir tablets, capsules (100 mg) or oral solution (80 mg/mL)	**Formulation: PREZISTA oral suspension (100 mg/mL) and ritonavir oral solution (80 mg/mL)**
Body weight (kg)	**Dose: twice daily with food**	**Dose: twice daily with food**
Greater than or equal to 15 kg to less than 30 kg	PREZISTA 375 mg with ritonavir 0.6 mL (48 mg)	PREZISTA 3.8 mL (375 mg)[b] with ritonavir 0.6 mL (48 mg)
Greater than or equal to 30 kg to less than 40 kg	PREZISTA 450 mg with ritonavir 0.75 mL (60 mg)	PREZISTA 4.6 mL (450 mg)[b] with ritonavir 0.75 mL (60 mg)
Greater than or equal to 40 kg	PREZISTA 600 mg with ritonavir 100 mg	PREZISTA 6 mL (600 mg) with ritonavir 1.25 mL (100 mg)

[a] darunavir resistance associated substitutions: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V

[b] The 375 mg and 450 mg dose using darunavir tablets for this weight group is rounded up to 3.8 mL and 4.6 mL for suspension dosing convenience.

The use of PREZISTA/ritonavir in pediatric patients below 3 years of age is not recommended *[see Warnings and Precautions (5.10) and Use in Specific Populations (8.4)]*.

2.6 Not Recommended in Patients with Severe Hepatic Impairment

No dosage adjustment is required in patients with mild or moderate hepatic impairment. No data are available regarding the use of PREZISTA/ritonavir when co-administered to subjects with severe hepatic impairment; therefore, PREZISTA/ritonavir 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

PREZISTA Oral Suspension

PREZISTA 100 mg per mL is supplied as a white to off-white opaque suspension for oral use, containing 100 mg of darunavir per mL of suspension.

PREZISTA Tablets

- 75 mg: white, caplet-shaped, film-coated tablets debossed with "75" on one side and "TMC" on the other side.
- 150 mg: white, oval-shaped, film-coated tablets debossed with "150" on one side and "TMC" on the other side.
- 600 mg: orange, oval-shaped, film-coated tablets debossed with "600MG" on one side and "TMC" on the other side.
- 800 mg: dark red, oval-shaped, film-coated tablets debossed with "800" on one side and "T" on the other side.

4 CONTRAINDICATIONS

Co-administration of PREZISTA/ritonavir 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). Examples of these drugs and other contraindicated drugs (which may lead to reduced efficacy of darunavir) are listed below *[see Drug Interactions (7.3)]*. Due to the need for co-administration of PREZISTA with ritonavir, please refer to ritonavir prescribing information for a description of ritonavir contraindications.

- Alpha 1-adrenoreceptor antagonist: alfuzosin
- Anti-gout: colchicine, in patients with renal and/or hepatic impairment
- Antimycobacterial: rifampin
- Antipsychotics: lurasidone, pimozide
- Cardiac Disorders: dronedarone, ivabradine, ranolazine
- Ergot derivatives, e.g. dihydroergotamine, ergotamine, methylergonovine
- Herbal product: St. John's wort (*Hypericum perforatum*)
- Hepatitis C direct acting antiviral: elbasvir/grazoprevir
- Lipid modifying agents: lomitapide, lovastatin, simvastatin
- Opioid Antagonist: naloxegol
- PDE-5 inhibitor: sildenafil when used for treatment of pulmonary arterial hypertension
- Sedatives/hypnotics: orally administered midazolam, triazolam

5 WARNINGS AND PRECAUTIONS

5.1 Importance of Co-administration with Ritonavir

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/ritonavir. During the clinical development program (N=3063), hepatitis was reported in 0.5% of patients receiving combination therapy with PREZISTA/ritonavir. 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/ritonavir therapy has not been established.

Appropriate laboratory testing should be conducted prior to initiating therapy with PREZISTA/ritonavir 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/ritonavir 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/ritonavir should prompt consideration of interruption or discontinuation of treatment.

5.3 Severe Skin Reactions

During the clinical development program (n=3063), severe skin reactions, accompanied by fever and/or elevations of transaminases in some cases, have been reported in 0.4% of subjects. Stevens-Johnson Syndrome was rarely (less than 0.1%) reported during the clinical development program. During post-marketing experience toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis have been reported. Discontinue PREZISTA/ritonavir immediately if signs or symptoms of severe skin reactions develop. These can include but are not limited to severe rash or rash accompanied with fever,

general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis and/or eosinophilia.

Rash (all grades, regardless of causality) occurred in 10.3% of subjects treated with PREZISTA/ritonavir *[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/ritonavir was 0.5%.

Rash occurred more commonly in treatment-experienced subjects receiving regimens containing PREZISTA/ritonavir + raltegravir compared to subjects receiving PREZISTA/ritonavir without raltegravir or raltegravir without PREZISTA/ritonavir. However, rash that was considered drug related occurred at similar rates for all three groups. These rashes were mild to moderate in severity and did not limit therapy; there were no discontinuations due to rash.

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/ritonavir, the incidence and severity of rash were similar in subjects with or without a history of sulfonamide allergy.

5.5 Risk of Serious Adverse Reactions due to Drug Interactions

Initiation of PREZISTA/ritonavir, a CYP3A inhibitor, in patients receiving medications metabolized by CYP3A or initiation of medications metabolized by CYP3A in patients already receiving PREZISTA/ritonavir, may increase plasma concentrations of medications metabolized by CYP3A and reduce plasma concentrations of active metabolite(s) formed by CYP3A.

Initiation of medications that inhibit or induce CYP3A may increase or decrease concentrations of PREZISTA/ritonavir, respectively.

These interactions may lead to:

- Clinically significant adverse reactions, potentially leading to severe, life threatening, or fatal events from greater exposures of concomitant medications.
- Clinically significant adverse reactions from greater exposures of PREZISTA/ritonavir.
- Loss of therapeutic effect of the concomitant medications from lower exposures of active metabolite(s).
- Loss of therapeutic effect of PREZISTA/ritonavir and possible development of resistance from lower exposures of PREZISTA/ritonavir.

See Table 10 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations *[see Drug Interactions (7)]*. Consider the potential for drug interactions prior to and during PREZISTA/ritonavir therapy; review concomitant medications during PREZISTA/ritonavir therapy; and monitor for the adverse reactions associated with the concomitant drugs *[see Contraindications (4) and Drug Interactions (7)]*.

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

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including PREZISTA. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, Guillain-Barré syndrome, and autoimmune hepatitis) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of antiretroviral 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 Not Recommended in Pediatric Patients Below 3 Years of Age

PREZISTA/ritonavir in pediatric patients below 3 years of age is not recommended 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 and 8.4) and Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of labeling:

- Hepatotoxicity *[see Warnings and Precautions (5.2)]*
- Severe Skin Reactions *[see Warnings and Precautions (5.3)]*
- Diabetes Mellitus/Hyperglycemia *[see Warnings and Precautions (5.6)]*
- Fat Redistribution *[see Warnings and Precautions (5.7)]*
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.8)]*
- Hemophilia *[see Warnings and Precautions (5.9)]*

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

6.1 Clinical Trials Experience

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 clinical practice.

Treatment Naïve-Adults: TMC114-C211

The safety assessment is based on all safety data from the Phase 3 trial TMC114-C211 comparing PREZISTA/ritonavir 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/ritonavir 800/100 mg once daily arm and in the lopinavir/ritonavir 800/200 mg per day arm was 162.5 and 153.5 weeks, respectively.

The majority of the adverse drug reactions (ADRs) reported during treatment with PREZISTA/ritonavir 800/100 mg once daily were mild in severity. The most common clinical ADRs to PREZISTA/ritonavir 800/100 mg once daily (greater than or equal to 5%) of at least moderate intensity (greater than or equal to Grade 2) were diarrhea, headache, abdominal pain and rash. 2.3% of subjects in the PREZISTA/ritonavir arm discontinued treatment due to ADRs.

ADRs to PREZISTA/ritonavir 800/100 mg once daily of at least moderate intensity (greater than or equal to Grade 2) in antiretroviral treatment-naïve HIV-1-infected adult subjects are presented in Table 6 and subsequent text below the table.

Table 6: Selected Clinical Adverse Drug Reactions to PREZISTA/ritonavir 800/100 mg Once Daily[a] of at Least Moderate Intensity (≥Grade 2) Occurring in ≥2% of Antiretroviral Treatment-Naïve HIV-1-Infected Adult Subjects (Trial TMC114-C211)

System organ class, preferred term, %	PREZISTA/ritonavir 800/100 mg once daily + TDF/FTC N=343	lopinavir/ritonavir 800/200 mg per day + TDF/FTC N=346
Gastrointestinal Disorders		
Abdominal pain	6%	6%

Diarrhea	9%	16%
Nausea	4%	4%
Vomiting	2%	4%
General Disorders and Administration Site Conditions		
Fatigue	<1%	3%
Metabolism and Nutrition Disorders		
Anorexia	2%	<1%
Nervous System Disorders		
Headache	7%	6%
Skin and Subcutaneous Tissue Disorders		
Rash	6%	7%

N=total number of subjects per treatment group; FTC=emtricitabine; TDF=tenofovir disoproxil fumarate
[a] Excluding laboratory abnormalities reported as ADRs.

Less Common Adverse Reactions

Treatment-emergent ADRs of at least moderate intensity (greater than or equal to Grade 2) occurring in less than 2% of antiretroviral treatment-naïve subjects receiving PREZISTA/ritonavir 800/100 mg once daily are listed below by body system:

Gastrointestinal Disorders: acute pancreatitis, dyspepsia, flatulence

General Disorders and Administration Site Conditions: asthenia

Hepatobiliary Disorders: acute hepatitis (e.g., acute hepatitis, cytolytic hepatitis, hepatotoxicity)

Immune System Disorders: (drug) hypersensitivity, immune reconstitution syndrome

Metabolism and Nutrition Disorders: diabetes mellitus

Musculoskeletal and Connective Tissue Disorders: myalgia, osteonecrosis

Psychiatric Disorders: abnormal dreams

Skin and Subcutaneous Tissue Disorders: angioedema, pruritus, Stevens-Johnson Syndrome, urticaria

Laboratory Abnormalities

Selected Grade 2 to 4 laboratory abnormalities that represent a worsening from baseline observed in antiretroviral treatment-naïve adult subjects treated with PREZISTA/ritonavir 800/100 mg once daily are presented in Table 7.

Table 7: Grade 2 to 4 Laboratory Abnormalities Observed in Antiretroviral Treatment-Naïve HIV-1-Infected Adult Subjects[a] (Trial TMC114-C211)

Laboratory parameter %	**Limit**	**PREZISTA/ritonavir 800/100 mg once daily + TDF/FTC**	**lopinavir/ritonavir 800/200 mg per day + TDF/FTC**
Biochemistry			
Alanine Aminotransferase			
Grade 2	>2.5 to ≤5.0 X ULN	9%	9%

Grade 3	>5.0 to ≤10.0 X ULN	3%	3%
Grade 4	>10.0 X ULN	<1%	3%
Aspartate Aminotransferase			
Grade 2	>2.5 to ≤5.0 X ULN	7%	10%
Grade 3	>5.0 to ≤10.0 X ULN	4%	2%
Grade 4	>10.0 X ULN	1%	3%
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%	5%
Grade 3	>2.5 to ≤5.0 X ULN	<1%	<1%
Grade 4	>5.0 X ULN	0%	0%
Triglycerides			
Grade 2	5.65-8.48 mmol/L 500-750 mg/dL	3%	10%
Grade 3	8.49-13.56 mmol/L 751-1200 mg/dL	2%	5%
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	23%	27%
Grade 3	>7.77 mmol/L >300 mg/dL	1%	5%
Low-Density Lipoprotein Cholesterol			
Grade 2	4.13-4.90 mmol/L 160-190 mg/dL	14%	12%
Grade 3	≥4.91 mmol/L ≥191 mg/dL	9%	6%
Elevated Glucose Levels			
Grade 2	6.95-13.88 mmol/L 126-250 mg/dL	11%	10%
Grade 3	13.89-27.75 mmol/L 251-500 mg/dL	1%	<1%
Grade 4	>27.75 mmol/L >500 mg/dL	0%	0%
Pancreatic Lipase			
Grade 2	>1.5 to ≤3.0 X ULN	3%	2%
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	5%	2%
Grade 3	>2.0 to ≤5.0 X ULN	5%	4%
Grade 4	>5.0 X ULN	0%	<1%

N=total number of subjects per treatment group; FTC=emtricitabine; TDF=tenofovir disoproxil fumarate

[a] Grade 4 data not applicable in Division of AIDS grading scale.

Treatment-Experienced Adults: TMC114-C214

The safety assessment is based on all safety data from the Phase 3 trial TMC114-C214 comparing PREZISTA/ritonavir 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/ritonavir 600/100 mg twice daily arm and in the lopinavir/ritonavir 400/100 mg twice daily arm was 80.7 and 76.4 weeks, respectively.

The majority of the ADRs reported during treatment with PREZISTA/ritonavir 600/100 mg twice daily were mild in severity. The most common clinical ADRs to PREZISTA/ritonavir 600/100 mg twice daily (greater than or equal to 5%) of at least moderate intensity (greater than or equal to Grade 2) were diarrhea, nausea, rash, abdominal pain and vomiting. 4.7% of subjects in the PREZISTA/ritonavir arm discontinued treatment due to ADRs.

ADRs to PREZISTA/ritonavir 600/100 mg twice daily of at least moderate intensity (greater than or equal to Grade 2) in antiretroviral treatment-experienced HIV-1-infected adult subjects are presented in Table 8 and subsequent text below the table.

Table 8: Selected Clinical Adverse Drug Reactions to PREZISTA/ritonavir 600/100 mg Twice Daily[a] of at Least Moderate Intensity (≥Grade 2) Occurring in ≥2% of Antiretroviral Treatment-Experienced HIV-1-Infected Adult Subjects (Trial TMC114-C214)

System organ class, preferred term, %	PREZISTA/ritonavir 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	6%	3%
Diarrhea	14%	20%
Dyspepsia	2%	1%
Nausea	7%	6%
Vomiting	5%	3%
General Disorders and Administration Site Conditions		
Asthenia	3%	1%
Fatigue	2%	1%
Metabolism and Nutrition Disorders		
Anorexia	2%	2%
Diabetes mellitus	2%	<1%
Nervous System Disorders		
Headache	3%	3%
Skin and Subcutaneous Tissue Disorders		
Rash	7%	3%

N=total number of subjects per treatment group; OBR=optimized background regimen

[a] Excluding laboratory abnormalities reported as ADRs.

Less Common Adverse Reactions

Treatment-emergent ADRs of at least moderate intensity (greater than or equal to Grade 2) occurring in less than 2% of antiretroviral treatment-experienced subjects receiving PREZISTA/ritonavir 600/100 mg twice daily are listed below by body system:

Gastrointestinal Disorders: acute pancreatitis, flatulence

Musculoskeletal and Connective Tissue Disorders: myalgia

Psychiatric Disorders: abnormal dreams

Skin and Subcutaneous Tissue Disorders: pruritus, urticaria

Laboratory Abnormalities

Selected Grade 2 to 4 laboratory abnormalities that represent a worsening from baseline observed in antiretroviral treatment-experienced adult subjects treated with PREZISTA/ritonavir 600/100 mg twice daily are presented in Table 9.

Table 9: Grade 2 to 4 Laboratory Abnormalities Observed in Antiretroviral Treatment-Experienced HIV-1-Infected Adult Subjects[a] (Trial TMC114-C214)

Laboratory parameter, %	Limit	PREZISTA/ritonavir 600/100 mg twice daily + OBR	lopinavir/ritonavir 400/100 mg twice daily + OBR
Biochemistry			
Alanine Aminotransferase			
Grade 2	>2.5 to ≤5.0 X ULN	7%	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	6%	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	<1%	2%
Grade 3	>2.5 to ≤5.0 X ULN	<1%	<1%
Grade 4	>5.0 X ULN	<1%	0%
Triglycerides			
Grade 2	5.65-8.48 mmol/L 500-750 mg/dL	10%	11%
Grade 3	8.49-13.56 mmol/L 751-1200 mg/dL	7%	10%
Grade 4	>13.56 mmol/L >1200 mg/dL	3%	6%
Total Cholesterol			
Grade 2	6.20-7.77 mmol/L 240-300 mg/dL	25%	23%
Grade 3	>7.77 mmol/L >300 mg/dL	10%	14%
Low-Density Lipoprotein Cholesterol			
Grade 2	4.13-4.90 mmol/L 160-190 mg/dL	14%	14%
Grade 3	≥4.91 mmol/L ≥191 mg/dL	8%	9%
Elevated Glucose Levels			
Grade 2	6.95-13.88 mmol/L 126-250 mg/dL	10%	11%

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	3%	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%	7%
Grade 3	>2.0 to ≤5.0 X ULN	7%	3%
Grade 4	>5.0 X ULN	0%	0%

N=total number of subjects per treatment group; OBR=optimized background regimen

[a] Grade 4 data not applicable in Division of AIDS grading scale.

Serious ADRs

The following serious ADRs of at least moderate intensity (greater than or equal to Grade 2) occurred in the Phase 2b and Phase 3 trials with PREZISTA/ritonavir: 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.

Patients Co-Infected with Hepatitis B and/or Hepatitis C Virus

In subjects co-infected with hepatitis B or C virus receiving PREZISTA/ritonavir, the incidence of adverse events and clinical chemistry abnormalities was not higher than in subjects receiving PREZISTA/ritonavir 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.

Clinical Trials Experience: Pediatric Patients

PREZISTA/ritonavir has been studied in combination with other antiretroviral agents in 3 Phase 2 trials. TMC114-C212, in which 80 antiretroviral treatment-experienced HIV-1-infected pediatric subjects 6 to less than 18 years of age and weighing at least 20 kg were included, TMC114-C228, in which 21 antiretroviral treatment-experienced HIV-1-infected pediatric subjects 3 to less than 6 years of age and weighing at least 10 kg were included, and TMC114-C230 in which 12 antiretroviral treatment-naïve HIV-1 infected pediatric patients aged from 12 to less than 18 years and weighing at least 40 kg were included. The TMC114-C212 and C228 trials evaluated PREZISTA/ritonavir twice daily dosing and the TMC114-C230 trial evaluated PREZISTA/ritonavir once daily dosing *[see Use in Specific Populations (8.4) and Clinical Studies (14.4)]*.

Frequency, type, and severity of ADRs in pediatric subjects were comparable to those observed in adults.

TMC114-C212

Clinical ADRs to PREZISTA/ritonavir (all grades, greater than or equal to 3%), were vomiting (13%), diarrhea (11%), abdominal pain (10%), headache (9%), rash (5%), nausea (4%), and fatigue (3%).

Grade 3 or 4 laboratory abnormalities were ALT increased (Grade 3: 3%; Grade 4: 1%), AST increased (Grade 3: 1%), pancreatic amylase increased (Grade 3: 4%, Grade 4: 1%), pancreatic lipase increased (Grade 3: 1%), total cholesterol increased (Grade 3: 1%), and LDL increased (Grade 3: 3%).

TMC114-C228

Clinical ADRs to PREZISTA/ritonavir (all grades, greater than or equal to 5%), were diarrhea (24%), vomiting (19%), rash (19%), abdominal pain (5%), and anorexia (5%).

There were no Grade 3 or 4 laboratory abnormalities considered as ADRs in this trial.

TMC114-C230

Clinical ADRs to PREZISTA/ritonavir (all grades, greater than or equal to 3%), were vomiting (33%), nausea (25%), diarrhea (16.7%), abdominal pain (8.3%), decreased appetite (8.3%), pruritus (8.3%), and rash (8.3%).

There were no Grade 3 or 4 laboratory abnormalities considered as ADRs in this trial.

6.2 Postmarketing Experience

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

Redistribution of body fat has been reported.

Rarely, rhabdomyolysis (associated with co-administration with HMG-CoA reductase inhibitors and PREZISTA/ritonavir) has been reported.

In addition, toxic epidermal necrolysis, acute generalized exanthematous pustulosis and drug rash with eosinophilia and systemic symptoms have been reported rarely *[see Warnings and Precautions (5.3)]*.

7 DRUG INTERACTIONS

7.1 Potential for PREZISTA/ritonavir to Affect Other Drugs

PREZISTA co-administered with ritonavir is an inhibitor of CYP3A, CYP2D6, and P-gp. Co-administration of PREZISTA and ritonavir with drugs that are primarily metabolized by CYP3A and CYP2D6 or are transported by P-gp may result in increased plasma concentrations of

such drugs, which could increase or prolong their therapeutic effect and adverse events. PREZISTA co-administered with ritonavir with drugs that have active metabolite(s) formed by CYP3A may result in reduced plasma concentrations of these active metabolite(s), potentially leading to loss of their therapeutic effect (see Table 10).

7.2 Potential for Other Drugs to Affect Darunavir

Darunavir and ritonavir are metabolized by CYP3A. *In vitro* data indicate that darunavir may be a P-gp substrate. 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, or P-gp may decrease the clearance of darunavir and ritonavir and may result in increased plasma concentrations of darunavir and ritonavir (see Table 10).

7.3 Established and Other Potentially Significant Drug Interactions

Table 10 provides dosing recommendations as a result of drug interactions with PREZISTA/ritonavir. 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. The table includes examples of potentially significant interactions but is not all inclusive *[see Contraindications (4) and Clinical Pharmacology (12.3)]*, and therefore the label of each drug that is co-administered with PREZISTA/ritonavir should be consulted for information related to the route of metabolism, interaction pathways, potential risks, and specific actions to be taken with regard to co-administration.

Table 10: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May be Recommended Based on Drug Interaction Studies or Predicted Interaction
(*see Contraindications (4)* for a list of examples of contraindicated drugs)
[*see Clinical Pharmacology (12.3)* for Magnitude of Interaction, Tables 15 and 16]

Concomitant Drug Class Drug Name Examples	**Effect on Concentration of Darunavir Or Concomitant Drug**	**Clinical Comment**
HIV-1-Antiviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
didanosine	↔ darunavir ↔ didanosine	Didanosine should be administered one hour before or two hours after PREZISTA/ritonavir (which are administered with food).
HIV-1-Antiviral Agents: HIV-Protease Inhibitors (PIs)		
indinavir (The reference regimen for indinavir was indinavir/ritonavir 800/100 mg twice daily.)	↑ darunavir ↑ indinavir	The appropriate dose of indinavir in combination with PREZISTA/ritonavir 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 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 ritonavir.
Other HIV protease inhibitors, except atazanavir *[see Drug Interactions (7.4)]*		As co-administration with PREZISTA/ritonavir has not been studied, co-administration is not recommended.
HIV-1-Antiviral Agents: CCR5 co-receptor antagonists		
maraviroc	↑ maraviroc	When used in combination with PREZISTA/ritonavir, the dose of maraviroc should be 150 mg twice daily.
Other Agents		
Alpha 1-adrenoreceptor antagonist: alfuzosin	↑ alfuzosin	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as hypotension.
Antibacterial: clarithromycin	↔ darunavir ↑ clarithromycin	No dose adjustment of the combination is required for patients with normal renal function. For co-administration of clarithromycin and PREZISTA/ritonavir in 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%.
Anticoagulants: Direct Oral Anticoagulants (DOACs) apixaban	↑ apixaban	Due to potentially increased bleeding risk, dosing recommendations for co-administration of apixaban with PREZISTA/ritonavir depend on the apixaban dose. Refer to apixaban dosing instructions for co-administration with P-gp and strong CYP3A inhibitors in apixaban prescribing information.
rivaroxaban	↑ rivaroxaban	Co-administration of PREZISTA/ritonavir and rivaroxaban is not recommended because it may lead to an increased bleeding risk.
dabigatran etexilate edoxaban	↑ dabigatran ↑ edoxaban	Refer to the dabigatran etexilate or edoxaban prescribing information for recommendations regarding co-administration. The specific recommendations are based on indication, renal function, and effect of the co-administered P-gp inhibitors on the concentration of dabigatran or edoxaban. Clinical monitoring is recommended when a DOAC not affected by CYP3A4 but transported by P-gp, including dabigatran etexilate

		and edoxaban, is co-administered with PREZISTA/ritonavir.
Other Anticoagulants warfarin	↓ warfarin ↔ darunavir	Warfarin concentrations are decreased when co-administered with PREZISTA/ritonavir. It is recommended that the international normalized ratio (INR) be monitored when warfarin is combined with PREZISTA/ritonavir.
Anticonvulsants: carbamazepine	↔ darunavir ↑ carbamazepine	The dose of either PREZISTA/ritonavir or carbamazepine does not need to be adjusted when initiating co-administration with PREZISTA/ritonavir and carbamazepine. Clinical monitoring of carbamazepine concentrations and its dose titration is recommended to achieve the desired clinical response.
clonazepam	↑ clonazepam	Clinical monitoring of anticonvulsants that are metabolized by CYP3A is recommended.
phenobarbital, phenytoin	↔ darunavir ↓ phenytoin ↓ phenobarbital	Phenytoin and phenobarbital levels should be monitored when co-administering with PREZISTA/ritonavir.
Antidepressants: Selective Serotonin Reuptake Inhibitors (SSRIs): paroxetine, sertraline	↓ paroxetine ↓ sertraline	If either sertraline or paroxetine is initiated in patients receiving PREZISTA/ritonavir, dose titrating the SSRI based on a clinical assessment of antidepressant response is recommended. Monitor for antidepressant response in patients on a stable dose of sertraline or paroxetine who start treatment with PREZISTA/ritonavir.
Tricyclic Antidepressants (TCAs): amitriptyline, desipramine, imipramine, nortriptyline	↑ amitriptyline ↑ desipramine ↑ imipramine ↑ nortriptyline	Use a lower dose of the tricyclic antidepressants and trazodone due to potential increased adverse events such as nausea, dizziness, hypotension and syncope.
Other: trazodone	↑ trazodone	
Antifungals: itraconazole, isavuconazole, ketoconazole, posaconazole	↑ darunavir ↑ itraconazole ↑ isavuconazole ↑ ketoconazole ↔ posaconazole	Monitor for increased PREZISTA/ritonavir and/or antifungal adverse events with concomitant use of these antifungals. When co-administration is required, the daily dose of ketoconazole or itraconazole should not exceed 200 mg with monitoring for increased antifungal adverse events.
voriconazole	↓ voriconazole	Voriconazole is not recommended for patients receiving PREZISTA/ritonavir unless an assessment comparing predicted benefit to risk ratio justifies the use of voriconazole.
Anti-gout:		

colchicine	↑ colchicine	Co-administration is contraindicated in patients with renal and/or hepatic impairment due to potential for serious and/or life-threatening reactions. For patients without renal or hepatic impairment: • Treatment of gout-flares – co-administration of colchicine in patients on PREZISTA/ritonavir: 0.6 mg (1 tablet) × 1 dose, followed by 0.3 mg (half tablet) 1 hour later. Treatment course to be repeated no earlier than 3 days. • Prophylaxis of gout-flares – co-administration of colchicine in patients on PREZISTA/ritonavir: If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day. If the original regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day. • Treatment of familial Mediterranean fever – co-administration of colchicine in patients on PREZISTA/ritonavir: maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
Antimalarial: artemether/lumefantrine	↓ artemether ↓ dihydroartemisinin ↑ lumefantrine ↔ darunavir	The combination of PREZISTA/ritonavir and artemether/lumefantrine can be used without dose adjustments. However, the combination should be used with caution as increased lumefantrine exposure may increase the risk of QT prolongation.
Antimycobacterials: rifampin	↓ darunavir	Co-administration is contraindicated due to potential for loss of therapeutic effect and development of resistance.
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.
rifapentine	↓ darunavir	Co-administration of PREZISTA/ritonavir with rifapentine is not recommended.
Antineoplastics: dasatinib, nilotinib	↑ antineoplastics	A decrease in the dosage or an adjustment of the dosing interval of dasatinib and nilotinib may be necessary for patients. Please refer to the dasatinib and nilotinib prescribing information for dosing instructions.
vinblastine, vincristine		For vincristine and vinblastine, consideration should be given to temporarily withholding the ritonavir-

		containing antiretroviral regimen in patients who develop significant hematologic or gastrointestinal side effects when PREZISTA/ritonavir is administered concurrently with vincristine or vinblastine. If the antiretroviral regimen must be withheld for a prolonged period, consideration should be given to initiating a revised regimen that does not include a CYP3A or P-gp inhibitor.
Antipsychotics: lurasidone	↑ lurasidone	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions.
pimozide	↑ pimozide	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
quetiapine	↑ quetiapine	Initiation of PREZISTA with ritonavir in patients taking quetiapine: Consider alternative antiretroviral therapy to avoid increases in quetiapine exposures. If co-administration is necessary, reduce the quetiapine dose to 1/6 of the current dose and monitor for quetiapine-associated adverse reactions. Refer to the quetiapine prescribing information for recommendations on adverse reaction monitoring. Initiation of quetiapine in patients taking PREZISTA with ritonavir: Refer to the quetiapine prescribing information for initial dosing and titration of quetiapine.
e.g. perphenazine, risperidone, thioridazine	↑ antipsychotics	A decrease in the dose of antipsychotics that are metabolized by CYP3A or CYP2D6 may be needed when co-administered with PREZISTA/ritonavir.
β-Blockers: e.g. carvedilol, metoprolol, timolol	↑ beta-blockers	Clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs when co-administered with PREZISTA/ritonavir and a lower dose of the beta blocker should be considered.
Calcium Channel Blockers: amlodipine, diltiazem, felodipine, nicardipine, nifedipine, verapamil	↑ calcium channel blockers	Clinical monitoring of patients is recommended.
Cardiac Disorders: ranolazine, ivabradine	↑ ranolazine ↑ ivabradine	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions.
dronedarone	↑ dronedarone	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Other antiarrhythmics e.g. amiodarone, bepridil, disopyramide, flecainide,	↑ antiarrhythmics	Therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when co-administered with PREZISTA/ritonavir.

lidocaine (systemic), mexiletine, propafenone, quinidine digoxin	↑ digoxin	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.
Corticosteroids: dexamethasone (systemic) Corticosteroids primarily metabolized by CYP3A: e.g. betamethasone budesonide ciclesonide fluticasone methylprednisolone mometasone triamcinolone	↓ darunavir ↑ corticosteroids	Co-administration of PREZISTA/ritonavir with systemic dexamethasone or other systemic corticosteroids that induce CYP3A may result in loss of therapeutic effect and development of resistance to darunavir. Consider alternative corticosteroids. Co-administration with corticosteroids (all routes of administration) of which exposures are significantly increased by strong CYP3A inhibitors can increase the risk for Cushing's syndrome and adrenal suppression. Alternative corticosteroids including beclomethasone, prednisone, and prednisolone (for which PK and/or PD are less affected by strong CYP3A inhibitors relative to other steroids) should be considered, particularly for long term use.
Endothelin receptor antagonist: bosentan	↑ bosentan	Co-administration of bosentan in patients on PREZISTA/ritonavir: In patients who have been receiving PREZISTA/ritonavir for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability. Co-administration of PREZISTA/ritonavir in patients on bosentan: Discontinue use of bosentan at least 36 hours prior to initiation of PREZISTA/ritonavir. After at least 10 days following the initiation of PREZISTA/ritonavir, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability.
Ergot derivatives: e.g. dihydroergotamine, ergotamine, methylergonovine	↑ ergot derivatives	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
Hepatitis C virus (HCV): Direct-Acting Antivirals: elbasvir/grazoprevir	↑ elbasvir/grazoprevir	Co-administration is contraindicated due to potential for the increased risk of alanine transaminase (ALT) elevations.

glecaprevir/pibrentasvir	↑ glecaprevir ↑ pibrentasvir	Co-administration of PREZISTA/ritonavir with glecaprevir/pibrentasvir is not recommended.
Herbal product: St. John's wort (*Hypericum perforatum*)	↓ darunavir	Co-administration is contraindicated due to potential for reduced plasma concentrations of darunavir, which may result in loss of therapeutic effect and development of resistance.
Hormonal contraceptives: ethinyl estradiol, norethindrone, drospirenone	 ↓ ethinyl estradiol ↓ norethindrone drospirenone: effects unknown	Effective alternative (non-hormonal) contraceptive method or a barrier method of contraception is recommended *[see Use in Specific Populations (8.3)]*. For co-administration with drospirenone, clinical monitoring is recommended due to the potential for hyperkalemia. No data are available to make recommendations on co-administration with other hormonal contraceptives.
Immunosuppressants: e.g. cyclosporine, tacrolimus, sirolimus **Immunosuppressant/neoplastic:** everolimus irinotecan	↑ immunosuppressants	Therapeutic concentration monitoring of the immunosuppressive agent is recommended when co-administered with PREZISTA/ritonavir. Co-administration of everolimus and PREZISTA/ritonavir is not recommended. Discontinue PREZISTA/ritonavir at least 1 week prior to starting irinotecan therapy. Do not administer PREZISTA/ritonavir with irinotecan unless there are no therapeutic alternatives.
Inhaled beta agonist: salmeterol	↑ salmeterol	Co-administration of salmeterol and PREZISTA/ritonavir is not recommended. The combination may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations and sinus tachycardia.
Lipid Modifying Agents: <u>HMG-CoA reductase inhibitors</u>: lovastatin, simvastatin atorvastatin, pravastatin, rosuvastatin <u>Other lipid modifying agents</u>: lomitapide	 ↑ lovastatin ↑ simvastatin ↑ HMG-CoA reductase inhibitors ↑ lomitapide	 Co-administration is contraindicated due to potential for serious reactions such as myopathy including rhabdomyolysis. Co-administration of PREZISTA/ritonavir with HMG-Co A reductase inhibitors may lead to adverse events such as myopathy. Titrate atorvastatin, pravastatin or rosuvastatin dose carefully and use the lowest necessary dose while monitoring for adverse events. Do not exceed atorvastatin 20 mg/day. Co-administration is contraindicated due to potential for markedly increased transaminases.

Narcotic analgesics metabolized by CYP3A: e.g. fentanyl, oxycodone	↑ fentanyl ↑ oxycodone	Careful monitoring of therapeutic effects and adverse reactions associated with CYP3A-metabolized narcotic analgesics (including potentially fatal respiratory depression) is recommended with co-administration.
tramadol	↑ tramadol	A dose decrease may be needed for tramadol with concomitant use.
Narcotic analgesics/treatment of opioid dependence: buprenorphine, buprenorphine/naloxone	↔ buprenorphine, naloxone ↑ norbuprenorphine (metabolite)	No dose adjustment for buprenorphine or buprenorphine/naloxone is required with concurrent administration of PREZISTA/ritonavir. Clinical monitoring is recommended if PREZISTA/ritonavir and buprenorphine or buprenorphine/naloxone are co-administered.
methadone	↓ methadone	No adjustment of methadone dosage is required when initiating co-administration of PREZISTA/ritonavir. However, clinical monitoring is recommended as the dose of methadone during maintenance therapy may need to be adjusted in some patients.
Opioid Antagonist naloxegol	↑ naloxegol	Co-administration of PREZISTA/ritonavir and naloxegol is contraindicated due to potential for precipitating opioid withdrawal symptoms.
PDE-5 inhibitors: e.g. avanafil, sildenafil, tadalafil, vardenafil	↑ PDE-5 inhibitors (only the use of sildenafil at doses used for treatment of erectile dysfunction has been studied with PREZISTA/ritonavir)	Co-administration with PREZISTA/ritonavir may result in an increase in PDE-5 inhibitor-associated adverse events, including hypotension, syncope, visual disturbances and priapism. <u>Use of PDE-5 inhibitors for pulmonary arterial hypertension (PAH):</u> Co-administration with sildenafil used for PAH is contraindicated due to potential for sildenafil associated adverse reactions (which include visual disturbances, hypotension, prolonged erection, and syncope). The following dose adjustments are recommended for use of tadalafil with PREZISTA/ritonavir: • <u>Co-administration of tadalafil in patients on PREZISTA/ritonavir:</u> In patients receiving PREZISTA/ritonavir for at least one week, start tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. • <u>Co-administration of PREZISTA/ritonavir in patients on tadalafil:</u> Avoid use of tadalafil during the initiation of PREZISTA/ritonavir. Stop tadalafil at least

		24 hours prior to starting PREZISTA/ritonavir. After at least one week following the initiation of PREZISTA/ritonavir, resume tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. Use of PDE-5 inhibitors for erectile dysfunction: 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. Co-administration of PREZISTA/ritonavir and avanafil is not recommended.
Platelet aggregation inhibitor: ticagrelor	↑ ticagrelor	Co-administration of PREZISTA/ritonavir and ticagrelor is not recommended.
clopidogrel	↓ clopidogrel active metabolite	Co-administration of PREZISTA/ritonavir and clopidogrel is not recommended due to potential reduction of the antiplatelet activity of clopidogrel.
prasugrel	↔ prasugrel active metabolite	No dose adjustment is needed when prasugrel is co-administered with PREZISTA/ritonavir.
Proton pump inhibitor: omeprazole	↓ omeprazole ↔ darunavir	When omeprazole is co-administered with PREZISTA/ritonavir, monitor patients for decreased efficacy of omeprazole. Consider increasing the omeprazole dose in patients whose symptoms are not well controlled; avoid use of more than 40 mg per day of omeprazole.
Sedatives/hypnotics: orally administered midazolam, triazolam	↑ midazolam ↑ triazolam	Co-administration is contraindicated due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression. Triazolam and orally administered midazolam are extensively metabolized by CYP3A. Co-administration of triazolam or orally administered midazolam with PREZISTA may cause large increases in the concentrations of these benzodiazepines.
metabolized by CYP3A e.g. buspirone, diazepam, estazolam, zolpidem	↑ sedatives/hypnotics	Titration is recommended when co-administering PREZISTA/ritonavir with sedatives/hypnotics metabolized by CYP3A and a lower dose of the sedatives/hypnotics should be considered with monitoring for adverse events.
parenterally administered midazolam		Co-administration of parenteral midazolam 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.
Urinary antispasmodics fesoterodine	↑ fesoterodine	When fesoterodine is co-administered with PREZISTA/ritonavir, do not exceed a fesoterodine dose of 4 mg once daily.
solifenacin	↑ solifenacin	When solifenacin is co-administered with PREZISTA/ritonavir, do not exceed a solifenacin dose of 5 mg once daily.

7.4 Drugs without Clinically Significant Interactions with PREZISTA

No dosage adjustments are recommended when PREZISTA/ritonavir is co-administered with the following medications: atazanavir, dolutegravir, efavirenz, etravirine, nevirapine, nucleoside reverse transcriptase inhibitors (abacavir, emtricitabine, emtricitabine/tenofovir alafenamide, lamivudine, stavudine, tenofovir disoproxil fumarate, zidovudine), pitavastatin, raltegravir, ranitidine, or rilpivirine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to PREZISTA during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) 1-800-258-4263.

Risk Summary

Prospective pregnancy data from the APR are not sufficient to adequately assess the risk of birth defects or miscarriage. Available limited data from the APR show no statistically significant difference in the overall risk of major birth defects for darunavir compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP*) [see Data]*.

The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the U.S. general population is 15-20%. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Studies in animals did not show evidence of developmental toxicity. Exposures (based on AUC) in rats were 3-fold higher, whereas in mice and rabbits, exposures were lower (less than 1-fold) than human exposures at the recommended daily dose *[see Data]*.

Clinical Considerations

The recommended dosage in pregnant patients is PREZISTA 600 mg taken with ritonavir 100 mg twice daily with food.

PREZISTA 800 mg taken with ritonavir 100 mg once daily should only be considered in certain pregnant patients who are already on a stable PREZISTA 800 mg with ritonavir 100 mg once daily regimen prior to pregnancy, are virologically suppressed (HIV-1 RNA less than 50 copies per mL), and in whom a change to twice daily PREZISTA 600 mg with ritonavir 100 mg may compromise tolerability or compliance *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

Data

Human Data

PREZISTA/ritonavir (600/100 mg twice daily or 800/100 mg once daily) in combination with a background regimen was evaluated in a clinical trial of 36 pregnant women during the second and third trimesters, and postpartum. Eighteen subjects were enrolled in each BID and QD treatment arms. Twenty-nine subjects completed the trial through the postpartum period (6-12 weeks after delivery) and 7 subjects discontinued before trial completion, 5 subjects in the BID arm and 2 subjects in the QD arm.

The pharmacokinetic data demonstrate that exposure to darunavir and ritonavir as part of an antiretroviral regimen was lower during pregnancy compared with postpartum (6-12 weeks). Exposure reductions during pregnancy were greater for the once daily regimen as compared to the twice daily regimen *[see Clinical Pharmacology (12.3)]*.

Virologic response was preserved. In the BID arm, the proportion of subjects with HIV-1 RNA <50 copies/mL were 39% (7/18) at baseline, 61% (11/18) through the third trimester visit, and 61% (11/18) through the 6-12 week postpartum visit. Virologic outcomes during the third trimester visit showed HIV-1 RNA ≥50 copies/mL for 11% (2/18) of subjects and were missing for 5 subjects (1 subject discontinued prematurely due to virologic failure). In the QD arm, the proportion of subjects with HIV-1 RNA <50 copies/mL were 61% (11/18) at baseline, 83% (15/18) through the third trimester visit, and 78% (14/18) through the 6-12 week postpartum visit. Virologic outcomes during the third trimester visit showed HIV-1 RNA ≥50 copies/mL for none of the subjects and were missing for 3 subjects (1 subject discontinued prematurely due to virologic failure).

PREZISTA/ritonavir was well tolerated during pregnancy and postpartum. There were no new clinically relevant safety findings compared with the known safety profile of PREZISTA/ritonavir in HIV-1-infected adults.

Among the 31 infants with HIV test results available data, born to the 31 HIV-infected pregnant women who completed trial through delivery or postpartum period, all 31 infants had test results that were negative for HIV-1 at the time of delivery and/or through 16 weeks postpartum. All 31 infants received antiretroviral prophylactic treatment containing zidovudine.

Based on prospective reports to the APR of over 980 exposures to darunavir-containing regimens during pregnancy resulting in live births (including over 660 exposed in the first trimester and over

320 exposed in the second/third trimester), the prevalence of birth defects in live births was 3.6% (95% CI: 2.3% to 5.3.%) with first trimester exposure to darunavir-containing regimens and 2.5% (95% CI: 1.1% to 4.8%) with second/third trimester exposure to darunavir-containing regimens.

Animal Data

Reproduction studies conducted with darunavir showed no embryotoxicity or teratogenicity in mice (doses up to 1000 mg/kg from gestation day (GD) 6-15 with darunavir alone) and rats (doses up to 1000 mg/kg from GD 7-19 in the presence or absence of ritonavir) as well as in rabbits (doses up to 1000 mg/kg/day from GD 8-20 with darunavir alone). In these studies, darunavir exposures (based on AUC) were higher in rats (3-fold), whereas in mice and rabbits, exposures were lower (less than 1-fold) compared to those obtained in humans at the recommended clinical dose of darunavir boosted with ritonavir.

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV.

There are no data on the presence of darunavir in human milk, the effects on the breastfed infant, or the effects on milk production. Darunavir is present in the milk of lactating rats *[see Data]*. Because of the potential for (1) HIV transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants) and (3) serious adverse reactions in a breastfed infant, instruct mothers not to breastfeed if they are receiving PREZISTA *[see Use in Specific Populations (8.4)]*.

Data

Animal Data

Studies in rats (with darunavir alone or with ritonavir) have demonstrated that darunavir is secreted in the milk. In the rat pre- and postnatal development study, a reduction in pup body weight gain was observed due to exposure of pups to drug substances via milk. The maximal maternal plasma exposures achieved with darunavir (up to 1000 mg/kg with ritonavir) were approximately 50% of those obtained in humans at the recommended clinical dose with ritonavir.

8.3 Females and Males of Reproductive Potential

Contraception

Use of PREZISTA may reduce the efficacy of combined hormonal contraceptives and the progestin only pill. Advise patients to use an effective alternative (non-hormonal) contraceptive method or add a barrier method of contraception. For co-administration with drospirenone, clinical monitoring is recommended due to the potential for hyperkalemia *[see Drug Interactions (7.3)]*.

8.4 Pediatric Use

PREZISTA/ritonavir is not recommended in pediatric patients below 3 years of age because 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 Warnings and Precautions (5.10), Use in Specific Populations (8.1) and Clinical Pharmacology (12.3)]*.

The safety, pharmacokinetic profile, and virologic and immunologic responses of PREZISTA/ritonavir administered twice daily were evaluated in treatment-experienced HIV-1-infected pediatric subjects 3 to less than 18 years of age and weighting at least 10 kg. These subjects were evaluated in clinical trials TMC114-C212 (80 subjects, 6 to less than 18 years of age) and TMC114-228 (21 subjects, 3 to less than 6 years of age) *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.4)]*. Frequency, type, and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adults *[see Adverse Reactions (6.1)]*. Refer to *Dosage and Administration (2.5)* for twice-daily dosing recommendations for pediatric subjects 3 to less than 18 years of age and weighing at least 10 kg.

In clinical trial TMC114-C230, the safety, pharmacokinetic profile and virologic and immunologic responses of PREZISTA/ritonavir administered once daily were evaluated in treatment-naïve HIV-1 infected pediatric subjects 12 to less than 18 years of age (12 subjects) *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.4)]*. Frequency, type, and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adults *[see Adverse Reactions (6.1)]*. Once daily dosing recommendations for pediatric patients 3 to less than 12 years of age were derived using population pharmacokinetic modeling and simulation. Although a PREZISTA/ritonavir once daily dosing pediatric trial was not conducted in children less than 12 years of age, there is sufficient clinical safety data to support the predicted PREZISTA exposures for the dosing recommendations in this age group *[see Clinical Pharmacology (12.3)]*. Please see *Dosage and Administration (2.5)* for once-daily dosing recommendations for pediatric subjects 3 to less than 18 years of age and weighing at least 10 kg.

Juvenile Animal Data

In a juvenile toxicity study where rats were directly dosed with darunavir (up to 1000 mg/kg), deaths occurred from post-natal day 5 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) 2 times the human plasma exposure levels.

8.5 Geriatric Use

Clinical studies of PREZISTA did not include sufficient numbers of patients aged 65 years 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 dosage adjustment of PREZISTA/ritonavir is necessary for patients with either mild or moderate hepatic impairment. No pharmacokinetic or safety data are available regarding the use

of PREZISTA/ritonavir in subjects with severe hepatic impairment. Therefore, PREZISTA/ritonavir is not recommended for use in patients with severe hepatic impairment *[see Dosage and Administration (2.6) 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)]*.

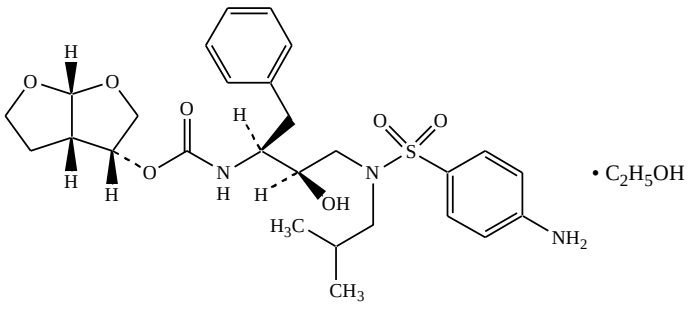
10 OVERDOSAGE

Human experience of acute overdose with PREZISTA/ritonavir is limited. 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. 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-1) protease.

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



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

PREZISTA® 100 mg per mL oral suspension is available as a white to off-white opaque suspension for oral administration.

Each mL of the oral suspension contains darunavir 100 mg (present as darunavir ethanolate). In addition, each mL contains the inactive ingredients citric acid monohydrate, hydrochloric acid (for pH adjustment), hydroxypropyl cellulose, masking flavor, methylparaben sodium, microcrystalline cellulose, purified water, sodium carboxymethylcellulose, strawberry cream flavor and sucralose.

PREZISTA® 75 mg tablets are available as white, caplet-shaped, film-coated tablets for oral administration. Each 75 mg tablet contains darunavir 75 mg (present as darunavir ethanolate).

PREZISTA® 150 mg tablets are available as white, oval-shaped, film-coated tablets for oral administration. Each 150 mg tablet contains darunavir 150 mg (present as darunavir ethanolate).

PREZISTA® 600 mg tablets are available as orange, oval-shaped, film-coated tablets for oral administration. Each 600 mg tablet contains darunavir 600 mg (present as darunavir ethanolate).

PREZISTA® 800 mg tablets are available as dark red, oval-shaped, film-coated tablets for oral administration. Each 800 mg tablet contains darunavir 800 mg (present as darunavir ethanolate).

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 800 mg tablet also contains hypromellose. The 75 and 150 mg tablet film coating, OPADRY® White, contains polyethylene glycol 3350, polyvinyl alcohol-partially hydrolyzed, talc, and titanium dioxide. The 600 mg tablet film coating, OPADRY® Orange, contains FD&C Yellow No. 6, polyethylene glycol 3350, polyvinyl alcohol-partially hydrolyzed, talc, and titanium dioxide. The 800 mg tablet film coating, OPADRY® Dark Red, contains iron oxide red, polyethylene glycol 3350, polyvinyl alcohol-partially hydrolyzed, talc, and titanium dioxide.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Darunavir is an HIV-1 antiviral drug *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In a thorough QT/QTc study in 40 healthy subjects, PREZISTA/ritonavir doses of 1.33 times the maximum recommended dose did not affect the QT/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), has been evaluated in healthy adult volunteers and in HIV-1-infected subjects. Table 11 displays the population pharmacokinetic estimates of darunavir after oral administration of PREZISTA/ritonavir 600/100 mg twice daily (based on sparse sampling in 285 patients in trial TMC114-C214, 278 patients in trial TMC114-C229 and 119 patients [integrated data] from trials TMC114-C202 and TMC114-C213) and PREZISTA/ritonavir 800/100 mg once daily (based on sparse sampling in 335 patients in trial TMC114-C211 and 280 patients in trial TMC114-C229) to HIV-1-infected patients.

Table 11: Population Pharmacokinetic Estimates of Darunavir at PREZISTA/ritonavir 800/100 mg Once Daily (Trial TMC114-C211, 48-Week Analysis and Trial TMC114-C229, 48-Week Analysis) and PREZISTA/ritonavir 600/100 mg Twice Daily (Trial TMC114-C214, 48-Week Analysis, Trial TMC114-C229, 48-Week Analysis and Integrated Data from Trials TMC114-C213 and TMC114-C202, Primary 24-Week Analysis)

	PREZISTA/ritonavir 800/100 mg once daily		PREZISTA/ritonavir 600/100 mg twice daily		
Parameter	**TMC114-C211 N=335**	**TMC114-C229 N=280**	**TMC114-C214 N=285**	**TMC114-C229 N=278**	**TMC114-C213 + TMC114-C202 (integrated data) N=119**
AUC_{24h} (ng.h/mL)[a]					
Mean ± Standard Deviation	93026 ± 27050	93334 ± 28626	116796 ± 33594	114302 ± 32681	124698 ± 32286
Median (Range)	87854 (45000-219240)	87788 (45456-236920)	111632 (64874-355360)	109401 (48934-323820)	123336 (67714-212980)
C_{0h} (ng/mL)					
Mean ± Standard Deviation	2282 ± 1168	2160 ± 1201	3490 ± 1401	3386 ± 1372	3578 ± 1151
Median (Range)	2041 (368-7242)	1896 (184-7881)	3307 (1517-13198)	3197 (250-11865)	3539 (1255-7368)

N=number of subjects with data

[a] 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 suggest that PREZISTA/ritonavir is an inhibitor of the P-glycoprotein (P-gp) transporters.

Effects of Food on Oral Absorption

When PREZISTA tablets were administered with food, the C_{max} and AUC of darunavir, co-administered with ritonavir, is approximately 40% higher relative to the fasting state. 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-1.

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/ritonavir 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 (2.6) 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-PREZISTA/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-1-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-1-infected females compared to males. This difference is not clinically relevant.

Race

Population pharmacokinetic analysis of darunavir in HIV-1-infected subjects indicated that race had no apparent effect on the exposure to darunavir.

Geriatric Patients

Population pharmacokinetic analysis in HIV-1-infected subjects showed that darunavir pharmacokinetics are not considerably different in the age range (18 to 75 years) evaluated in HIV-1-infected subjects (n=12, age greater than or equal to 65) *[see Use in Specific Populations (8.5)]*.

Pediatric Patients

PREZISTA/ritonavir administered twice daily

The pharmacokinetics of darunavir in combination with ritonavir in 93 antiretroviral treatment-experienced HIV-1-infected pediatric subjects 3 to less than 18 years of age and weighing at least 10 kg showed that the administered weight-based dosages resulted in similar darunavir exposure when compared to the darunavir exposure achieved in treatment-experienced adults receiving PREZISTA/ritonavir 600/100 mg twice daily *[see Dosage and Administration (2.5)]*.

PREZISTA/ritonavir administered once daily

The pharmacokinetics of darunavir in combination with ritonavir in 12 antiretroviral treatment-naïve HIV-1-infected pediatric subjects 12 to less than 18 years of age and weighing at least 40 kg receiving PREZISTA/ritonavir 800/100 mg once daily resulted in similar darunavir exposures when compared to the darunavir exposure achieved in treatment-naïve adults receiving PREZISTA/ritonavir 800/100 mg once daily *[see Dosage and Administration (2.5)]*.

Based on population pharmacokinetic modeling and simulation, the proposed PREZISTA/ritonavir once daily dosing regimens for pediatric patients 3 to less than 12 years of age is predicted to result in similar darunavir exposures when compared to the darunavir exposures achieved in treatment-naïve adults receiving PREZISTA/ritonavir 800/100 mg once daily *[see Dosage and Administration (2.5)]*.

The population pharmacokinetic parameters in pediatric subjects with PREZISTA/ritonavir administered once or twice daily are summarized in the table below:

Table 12: Population Pharmacokinetic Estimates of Darunavir Exposure (Trials TMC114-C230, TMC114-C212 and TMC114-C228) Following Administration of Doses in Tables 2 and 3

	PREZISTA/ritonavir once daily	**PREZISTA/ritonavir twice daily**		
			TMC114-C228[c]	
Parameter	**TMC114-C230[a] N=12**	**TMC114-C212 N=74**	**10 to less than 15 kg[b] N=10**	**15 to less than 20 kg[d] N=13**
AUC_{24h} (ng·h/mL)[e])				
Mean ± Standard Deviation	84390 ± 23587	126377 ± 34356	137896 ± 51420	157760 ± 54080
Median (Range)	86741 (35527–123325)	127340 (67054–230720)	124044 (89688–261090)	132698 (112310–294840)
C_{0h} (ng/mL)				
Mean ± Standard Deviation	2141 ± 865	3948 ± 1363	4510 ± 2031	4848 ± 2143
Median (Range)	2234 (542–3776)	3888 (1836–7821)	4126 (2456–9361)	3927 (3046–10292)

N=number of subjects with data.

[a] Summary statistics for population pharmacokinetic parameter estimates for DRV after administration of DRV/rtv at 800/100 mg once daily in treatment-naïve HIV-1 infected subjects from 12 to <18 years of age – Week-48 Analyses.

[b] Calculated from individual pharmacokinetic parameters estimated for Week 2 and Week 4, based on the Week 48 analysis that evaluated a darunavir dose of 20 mg/kg twice daily with ritonavir 3 mg/kg twice daily.

[c] Subjects may have contributed pharmacokinetic data to both the 10 kg to less than 15 kg weight group and the 15 kg to less than 20 kg weight group.

[d] The 15 kg to less than 20 kg weight group received 380 mg (3.8 mL) PREZISTA oral suspension twice daily with 48 mg (0.6 mL) ritonavir oral solution twice daily in TMC114-C228. Calculated from individual pharmacokinetic parameters estimated for Week 2 post-dose adjustment visit; Week 24 and Week 48 based on the – Week 48 analysis that evaluated a darunavir dose of 380 mg twice daily.

[e] AUC_{24h} is calculated as AUC_{12h}*2.

Pregnancy and Postpartum

The exposure to total darunavir and ritonavir after intake of PREZISTA/ritonavir 600/100 mg twice daily and PREZISTA/ritonavir 800/100 mg once daily as part of an antiretroviral regimen was generally lower during pregnancy compared with postpartum (see Table 13, Table 14 and Figure 1).

Table 13: Pharmacokinetic Results of Total Darunavir After Administration of PREZISTA/ritonavir at 600/100 mg Twice Daily as Part of an Antiretroviral Regimen, During the 2nd Trimester of Pregnancy, the 3rd Trimester of Pregnancy and Postpartum

Pharmacokinetics of total darunavir (mean ± standard deviation)	**2nd Trimester of pregnancy (n=12)[a]**	**3rd Trimester of pregnancy (n=12)**	**Postpartum (6-12 Weeks) (n=12)**
C_{max}, ng/mL	4668 ± 1097	5328 ± 1631	6659 ± 2364

AUC_{24h}, ng.h/mL[b]	78740 ± 19194	91760 ± 34720	113780 ± 52680
C_{min}, ng/mL	1922 ± 825	2661 ± 1269	2851 ± 2216

[a] n=11 for AUC_{24h}

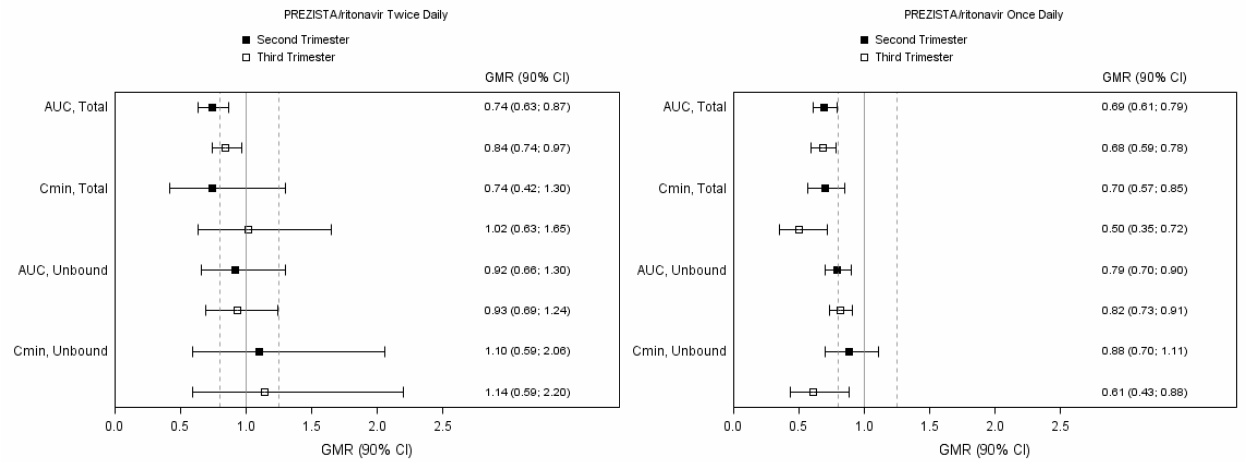
[b] AUC_{24h} is calculated as AUC_{12h}*2.

Table 14: Pharmacokinetic Results of Total Darunavir After Administration of PREZISTA/ritonavir at 800/100 mg Once Daily as Part of an Antiretroviral Regimen, During the 2nd Trimester of Pregnancy, the 3rd Trimester of Pregnancy and Postpartum

Pharmacokinetics of total darunavir (mean ± standard deviation)	**2nd Trimester of pregnancy (n=17)**	**3rd Trimester of pregnancy (n=15)**	**Postpartum (6-12 Weeks) (n=16)**
C_{max}, ng/mL	4964 ± 1505	5132 ± 1198	7310 ± 1704
AUC_{24h}, ng.h/mL	62289 ± 16234	61112 ± 13790	92116 ± 29241
C_{min}, ng/mL	1248 ± 542	1075 ± 594	1473 ± 1141

Due to an increase in the unbound fraction of darunavir during pregnancy compared to postpartum, unbound darunavir exposures were less reduced during pregnancy as compared to postpartum. Exposure reductions during pregnancy were greater for the once daily regimen as compared to the twice daily regimen (see Figure 1).

Figure 1: Pharmacokinetic Results (Within-Subject Comparison) of Total and Unbound Darunavir After Administration of PREZISTA/ritonavir at 600/100 mg Twice Daily or 800/100 mg Once Daily as Part of an Antiretroviral Regimen, During the 2nd and 3rd Trimester of Pregnancy Compared to Postpartum



Legend: 90% CI: 90% confidence interval; GMR: geometric mean ratio. Solid vertical line: ratio of 1.0; dotted vertical lines: reference lines of 0.8 and 1.25.

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, CYP2D6, and P-gp. Co-administration of darunavir and ritonavir with drugs primarily metabolized by CYP3A and CYP2D6, or are transported by P-gp, 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. *In vitro* data indicate that darunavir may be a P-gp substrate. 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 or P-gp 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 15 (effect of other drugs on darunavir) and Table 16 (effect of darunavir on other drugs). For information regarding clinical recommendations, *see Drug Interactions (7).*

Several interaction studies have been performed with a dose other than the recommended dose of the co-administered drug or darunavir; however, the results are applicable to the recommended dose of the co-administered drug and/or darunavir.

Table 15: 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 HIV protease inhibitors							
Atazanavir	300 mg q.d.[a]	400/100 mg b.i.d.[b]	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.[c]	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.[c]	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 HIV 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[d] (1.14-1.73)	1.24[d] (0.97-1.57)	1.02[d] (0.79-1.32)
Rilpivirine	150 mg q.d.	800/100 mg q.d.	15	↔	0.90 (0.81-1.00)	0.89 (0.81-0.99)	0.89 (0.68-1.16)

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							
Artemether/ lumefantrine	80/480 mg (6 doses at 0, 8, 24, 36, 48, and 60 hours)	600/100 mg b.i.d.	14	↔	1.00 (0.93-1.07)	0.96 (0.90-1.03)	0.87 (0.77-0.98)
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)
Pitavastatin	4 mg q.d.	800/100 mg q.d.	27	↔	1.06 (1.00-1.12)	1.03 (0.95-1.12)	NA
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.[e]	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

[a] q.d. = once daily

[b] b.i.d. = twice daily

[c] The pharmacokinetic parameters of darunavir in this study were compared with the pharmacokinetic parameters following administration of PREZISTA/ritonavir 600/100 mg twice daily.

[d] Ratio based on between-study comparison.

[e] q.o.d. = every other day

Table 16: Drug Interactions: Pharmacokinetic Parameters for Co-Administered Drugs in the Presence of PREZISTA/ritonavir

	Dose/Schedule				**LS Mean ratio (90% CI) of co-administered drug pharmacokinetic parameters with/without darunavir no effect =1.00**		
Co-administered drug	**Co-administered drug**	**Darunavir/ ritonavir**	**N**	**PK**	**C_{max}**	**AUC**	**C_{min}**
Co-administration with other HIV protease inhibitors							
Atazanavir	300 mg q.d.[a] /100 mg ritonavir q.d. when administered alone 300 mg q.d. when administered with darunavir/ ritonavir	400/100 mg b.i.d.[b]	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.	400/100 mg b.i.d.	9	↑	1.08	1.23	2.25 (1.63-3.10)

	/100 mg ritonavir b.i.d. when administered alone 800 mg b.i.d. when administered with darunavir/ ritonavir				(0.95-1.22)	(1.06-1.42)	
Lopinavir/ritonavir	400/100 mg b.i.d.[c] 533/133.3 mg b.i.d..[c]	1200/100 mg b.i.d. 1200 mg b.i.d.	14 15	↔ ↔	0.98 (0.78-1.22) 1.11 (0.96-1.30)	1.09 (0.86-1.37) 1.09 (0.96-1.24)	1.23 (0.90-1.69) 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 HIV 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)	-
Dolutegravir	30 mg q.d	600/100 mg b.i.d.	15	↓	0.89 (0.83-0.97)	0.78 (0.72-0.85)	0.62[d] (0.56-0.69)
Dolutegravir	50 mg q.d.	600/100 mg b.i.d. with 200 mg b.i.d. etravirine	9	↓	0.88 (0.78-1.00)	0.75 (0.69-0.81)	0.63[d] (0.52-0.76)
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 (0.57-0.82)	0.63 (0.54-0.73)	0.51 (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)
Rilpivirine	150 mg q.d.	800/100 mg q.d.	14	↑	1.79 (1.56-2.06)	2.30 (1.98-2.67)	2.78 (2.39-3.24)
Tenofovir disoproxil fumarate	300 mg q.d.	300/100 mg b.i.d.	12	↑	1.24 (1.08-1.42)	1.22 (1.10-1.35)	1.37 (1.19-1.57)
Maraviroc	150 mg b.i.d.	600/100 mg b.i.d.	12	↑	2.29 (1.46-3.59)	4.05 (2.94-5.59)	8.00 (6.35-10.1)

		600/100 mg b.i.d. with 200 mg b.i.d. etravirine	10	↑	1.77 (1.20-2.60)	3.10 (2.57-3.74)	5.27 (4.51-6.15)
Co-administration with other drugs							
Atorvastatin	40 mg q.d. when administered alone 10 mg q.d. when administered with darunavir/ritonavir	300/100 mg b.i.d.	15	↑	0.56 (0.48-0.67)	0.85 (0.76-0.97)	1.81 (1.37-2.40)
Artemether Dihydroartemisinin	80 mg single dose	600/100 mg b.i.d.	15	↓	0.85 (0.68-1.05)	0.91 (0.78-1.06)	-
			15	↑	1.06 (0.82-1.39)	1.12 (0.96-1.30)	-
Artemether Dihydroartemisinin Lumefantrine	artemether/ lumefantrine 80/480 mg (6 doses at 0, 8, 24, 36, 48, and 60 hours)	600/100 mg b.i.d.	15	↓	0.82 (0.61-1.11)	0.84 (0.69-1.02)	0.97 (0.90-1.05)
			15	↓	0.82 (0.66-1.01)	0.82 (0.74-0.91)	1.00 (0.82-1.22)
			15	↑	1.65 (1.49-1.83)	2.75 (2.46-3.08)	2.26 (1.92-2.67)
Buprenorphine/ Naloxone Norbuprenorphine	8/2 mg to 16/4 mg q.d.	600/100 mg b.i.d.	17 17	↔ ↑	0.92[e] (0.79-1.08) 1.36 (1.06-1.74)	0.89[e] (0.78-1.02) 1.46 (1.15-1.85)	0.98[e] (0.82-1.16) 1.71 (1.29-2.27)
Carbamazepine Carbamazepine epoxide	200 mg b.i.d.	600/100 mg b.i.d.	16 16	↑ ↓	1.43 (1.34-1.53) 0.46 (0.43-0.49)	1.45 (1.35-1.57) 0.46 (0.44-0.49)	1.54 (1.41-1.68) 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)
Dabigatran etexilate	150 mg	800/100 mg single dose 800/100 mg q.d.[f]	14 13	↑ ↑	1.64 (1.21-2.23) 1.22 (0.89-1.67)	1.72 (1.33-2.23) 1.18 (0.90-1.53)	- -
Dextromethorphan Dextrorphan	30 mg	600/100 mg b.i.d.	12	↑ ↓	2.27 (1.59-3.26)	2.70 (1.80-4.05)	- -

					0.87 (0.77-0.98)	0.96 (0.90-1.03)	
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) Norethindrone (NE)	Ortho-Novum 1/35 (35 µg EE /1 mg NE)	600/100 mg b.i.d.	11 11	↓ ↓	0.68 (0.61-0.74) 0.90 (0.83-0.97)	0.56 (0.50-0.63) 0.86 (0.75-0.98)	0.38 (0.27-0.54) 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 5-hydroxy omeprazole	40 mg single dose	600/100 mg b.i.d.	12	↓ ↓	0.66 (0.48-0.90) 0.93 (0.71-1.21)	0.58 (0.50-0.66) 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)
Pitavastatin	4 mg q.d.	800/100 mg q.d.	27	↓	0.96 (0.84-1.09)	0.74 (0.69-0.80)	NA
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 25-*O*-desacetyl-rifabutin	150 mg q.o.d.[g] when administered with PREZISTA/ ritonavir 300 mg q.d. when administered alone	600/100 mg b.i.d.[h]	11 11	↑ ↑	0.72 (0.55-0.93) 4.77 (4.04-5.63)	0.93 (0.80-1.09) 9.81 (8.09-11.9)	1.64 (1.48-1.81) 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/	400/100 mg b.i.d.	16	↑	0.62 (0.55-0.70)	0.97 (0.86-1.09)	-

	ritonavir						
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

[a] q.d. = once daily

[b] b.i.d. = twice daily

[c] The pharmacokinetic parameters of lopinavir in this study were compared with the pharmacokinetic parameters following administration of lopinavir/ritonavir 400/100 mg twice daily.

[d] Noted as C_{τ} or C_{24} in the dolutegravir U.S. prescribing information

[e] Ratio is for buprenorphine; mean C_{max} and AUC_{24} for naloxone were comparable when buprenorphine/naloxone was administered with or without PREZISTA/ritonavir

[f] 800/100 mg q.d. for 14 days before co-administered with dabigatran etexilate.

[g] q.o.d. = every other day

[h] In comparison to rifabutin 300 mg once daily.

12.4 Microbiology

Mechanism of Action

Darunavir is an inhibitor of the HIV-1 protease. It selectively inhibits the cleavage of HIV-1 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 less than 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, rilpivirine, 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 PREZISTA/ritonavir. Darunavir-resistant virus derived in cell culture from wild-type HIV-1 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 trials of PREZISTA/ritonavir in treatment-experienced subjects: In a pooled analysis of the 600/100 mg PREZISTA/ritonavir twice daily arms of trials TMC114-C213, TMC114-C202, TMC114-C215, and the control arms of etravirine trials TMC125-C206 and TMC125-C216, the amino acid substitutions V32I and I54L or M developed most frequently on PREZISTA/ritonavir in 41% and 25%, respectively, of the treatment-experienced subjects who experienced virologic failure, either by rebound or by never being suppressed (less than 50 copies/mL). Other substitutions that developed frequently in PREZISTA/ritonavir virologic failure isolates occurred at amino acid positions V11I, I15V, L33F, I47V, I50V, and L89V. These amino acid substitutions were associated with decreased susceptibility to darunavir; 90% of the virologic failure isolates had a greater than 7-fold decrease in susceptibility to darunavir at failure. The median darunavir phenotype (fold change from reference) of the virologic failure isolates was 4.3-fold at baseline and 85-fold at failure. Amino acid substitutions were also observed in the protease cleavage sites in the Gag polyprotein of some PREZISTA/ritonavir virologic failure isolates. In trial TMC114-C212 of treatment-experienced pediatric subjects, the amino acid substitutions V32I, I54L and L89M developed most frequently in virologic failures on PREZISTA/ritonavir.

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

In the 48-week analysis of the Phase 3 trial TMC114-C229, the number of virologic failures (including those who discontinued before suppression after Week 4) was 26% (75/294) in the group of subjects receiving PREZISTA/ritonavir 800/100 mg once daily compared to 19%

(56/296) of subjects receiving PREZISTA/ritonavir 600/100 mg twice daily. Examination of isolates from subjects who failed on PREZISTA/ritonavir 800/100 mg once daily and had post-baseline genotypes showed that 8 subjects (8/60; 13%) had isolates that developed IAS-USA defined PI resistance-associated substitutions compared to 5 subjects (5/39; 13%) on PREZISTA/ritonavir 600/100 mg twice daily. Isolates from 2 subjects developed PI resistance associated substitutions associated with decreased susceptibility to darunavir; 1 subject isolate in the PREZISTA/ritonavir 800/100 mg once daily arm, developed substitutions V32I, M46I, L76V and I84V associated with a 24-fold decreased susceptibility to darunavir, and 1 subject isolate in the PREZISTA/ritonavir 600/100 mg twice daily arm developed substitutions L33F and I50V associated with a 40-fold decreased susceptibility to darunavir. In the PREZISTA/ritonavir 800/100 mg once daily and PREZISTA/ritonavir 600/100 mg twice daily groups, isolates from 7 (7/60; 12%) and 4 (4/42; 10%) virologic failures, respectively, developed decreased susceptibility to an NRTI included in the treatment regimen.

Clinical trials of PREZISTA/ritonavir in treatment-naïve subjects: In the 192-week as-treated analysis censoring those who discontinued before Week 4 of the Phase 3 trial TMC114-C211, the percentage of virologic failures (never suppressed, rebounders and discontinued before achieving suppression) was 22% (64/288) in the group of subjects receiving PREZISTA/ritonavir 800/100 mg once daily compared to 29% (76/263) of subjects receiving lopinavir/ritonavir 800/200 mg per day. In the PREZISTA/ritonavir arm, emergent PI resistance-associated substitutions were identified in 11 of the virologic failures with post-baseline genotypic data (n=43). However, none of the darunavir virologic failures had a decrease in darunavir susceptibility (greater than 7-fold change) at failure. In the comparator lopinavir/ritonavir arm, emergent PI resistance-associated substitutions were identified in 17 of the virologic failures with post-baseline genotypic data (n=53), but none of the lopinavir/ritonavir virologic failures had decreased susceptibility to lopinavir (greater than 10-fold change) at failure. The reverse transcriptase M184V substitution and/or resistance to emtricitabine, which was included in the fixed background regimen, was identified in 4 virologic failures from the PREZISTA/ritonavir arm and 7 virologic failures in the lopinavir/ritonavir arm.

Cross-resistance

Cross-resistance among PIs has been observed. Darunavir has a less than 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 less than 3 for tipranavir, indicative of limited cross-resistance between darunavir and tipranavir. In trials TMC114-C213, TMC114-C202, and TMC114-C215, 34% (64/187) of subjects in the PREZISTA/ritonavir arm whose baseline isolates had decreased susceptibility to tipranavir (tipranavir fold change greater than 3) achieved less than 50 copies/mL serum HIV-1 RNA levels

at Week 96. Of the viruses isolated from subjects experiencing virologic failure on PREZISTA/ritonavir 600/100 mg twice daily (greater than 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 trial TMC114-C214, the 7 PREZISTA/ritonavir virologic failures with reduced susceptibility to darunavir at failure were also resistant to the approved PIs (fos)amprenavir, atazanavir, lopinavir, indinavir, and nelfinavir at failure. Six of these 7 were resistant to saquinavir and 5 were resistant to tipranavir. Four of these virologic failures were already PI-resistant at baseline.

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

Baseline Genotype/Phenotype and Virologic Outcome Analyses

Genotypic and/or phenotypic analysis of baseline virus may aid in determining darunavir susceptibility before initiation of PREZISTA/ritonavir 600/100 mg twice daily therapy. The effect of baseline genotype and phenotype on virologic response at 96 weeks was analyzed in as-treated analyses using pooled data from the Phase 2b trials (Trials 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 trials 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 17).

Table 17: Response to PREZISTA/ritonavir 600/100 mg Twice Daily by Baseline Number of IAS-Defined Primary PI Resistance-Associated Substitutions: As-treated Analysis of Trials TMC114-C213, TMC114-C202, and TMC114-C215

# IAS-defined primary PI substitutions	Proportion of subjects with <50 copies/mL at Week 96 N=439		
	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)

ENF=enfuvirtide

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

The presence at baseline of two or more of the substitutions V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V or L89V was associated with a decreased virologic response to

PREZISTA/ritonavir. In subjects not taking enfuvirtide *de novo*, the proportion of subjects achieving viral load less than 50 plasma HIV-1 RNA copies/mL at 96 weeks was 59%, 29%, and 12% when the baseline genotype had 0-1, 2 and greater than or equal to 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 18. These baseline phenotype groups are based on the select patient populations in the trials TMC114-C213, TMC114-C202, and TMC114-C215, and are not meant to represent definitive clinical susceptibility breakpoints for PREZISTA/ritonavir. The data are provided to give clinicians information on the likelihood of virologic success based on pre-treatment susceptibility to darunavir.

Table 18: Response (HIV-1 RNA <50 copies/mL at Week 96) to PREZISTA/ritonavir 600/100 mg Twice Daily by Baseline Darunavir Phenotype and by Use of Enfuvirtide: As-treated Analysis of Trials TMC114-C213, TMC114-C202, and TMC114-C215

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

ENF=enfuvirtide

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, 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 was 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.

14 CLINICAL STUDIES

14.1 Description of Adult Clinical Trials

The evidence of efficacy of PREZISTA/ritonavir is based on the analyses of 192-week data from a randomized, controlled open-label Phase 3 trial in treatment-naïve (TMC114-C211) HIV-1-infected adult subjects and 96-week data from a randomized, controlled, open-label Phase 3 trial in antiretroviral treatment-experienced (TMC114-C214) HIV-1-infected adult subjects. In addition, 96-week data are included from 2 randomized, controlled Phase 2b trials, TMC114-C213 and TMC114-C202, in antiretroviral treatment-experienced HIV-1-infected adult subjects.

14.2 Treatment-Naïve Adult Subjects

TMC114-C211

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

HIV-1-infected subjects who were eligible for this trial had plasma HIV-1 RNA greater than or equal to 5000 copies/mL. Randomization was stratified by screening plasma viral load (HIV-1 RNA less than 100,000 copies/mL or greater than or equal to 100,000 copies/mL) and screening CD4+ cell count (less than 200 cells/mm^3 or greater than or equal to 200 cells/mm^3). Virologic response was defined as a confirmed plasma HIV-1 RNA viral load less than 50 copies/mL. Analyses included 689 subjects in trial TMC114-C211 who had completed 192 weeks of treatment or discontinued earlier.

Demographics and baseline characteristics were balanced between the PREZISTA/ritonavir arm and the lopinavir/ritonavir arm (see Table 19). Table 19 compares the demographic and baseline characteristics between subjects in the PREZISTA/ritonavir 800/100 mg once daily arm and subjects in the lopinavir/ritonavir 800/200 mg per day arm in trial TMC114-C211.

Table 19: Demographic and Baseline Characteristics of Subjects in Trial TMC114-C211

	PREZISTA/ritonavir 800/100 mg once daily + TDF/FTC N=343	**lopinavir/ritonavir 800/200 mg per day + TDF/FTC N=346**
Demographic characteristics		
Median age (years) (range, years)	34 (18-70)	33 (19-68)
Sex		
Male	70%	70%
Female	30%	30%
Race		
White	40%	45%

Black	23%	21%
Hispanic	23%	22%
Asian	13%	11%
Baseline characteristics		
Mean baseline plasma HIV-1 RNA (log_{10} copies/mL)	4.86	4.84
Median baseline CD4+ cell count (cells/mm^3) (range, cells/mm^3)	228 (4-750)	218 (2-714)
Percentage of patients with baseline viral load ≥100,000 copies/mL	34%	35%
Percentage of patients with baseline CD4+ cell count <200 cells/mm^3	41%	43%

FTC=emtricitabine; TDF=tenofovir disoproxil fumarate

Week 192 outcomes for subjects on PREZISTA/ritonavir 800/100 mg once daily from trial TMC114-C211 are shown in Table 20.

Table 20: Virologic Outcome of Randomized Treatment of Trial TMC114-C211 at 192 Weeks

	PREZISTA/ritonavir 800/100 mg once daily + TDF/FTC N=343	**lopinavir/ritonavir 800/200 mg per day + TDF/FTC N=346**
Virologic success HIV-1 RNA <50 copies/mL	70%[a]	61%
Virologic failure[b]	12%	15%
No virologic data at Week 192 window[c]		
Reasons		
Discontinued trial due to adverse event or death[d]	5%	13%
Discontinued trial for other reasons[e]	13%	12%
Missing data during window[c] but on trial	<1%	0%

N = total number of subjects with data; FTC=emtricitabine; TDF=tenofovir disoproxil fumarate

[a] 95% CI: 1.9; 16.1

[b] Includes patients who discontinued prior to Week 192 for lack or loss of efficacy and patients who are ≥50 copies in the 192-week window and patients who had a change in their background regimen that was not permitted by the protocol.

[c] Window 186-198 Weeks.

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

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

In trial TMC114-C211 at 192 weeks of treatment, the median increase from baseline in CD4+ cell counts was 258 cells/mm^3 in the PREZISTA/ritonavir 800/100 mg once daily arm and 263 cells/mm^3 in the lopinavir/ritonavir 800/200 mg per day arm. Of the PREZISTA/ritonavir subjects with a confirmed virologic response of <50 copies/mL at Week 48, 81% remained undetectable at Week 192 versus 68% with lopinavir/ritonavir. In the 192 week analysis, statistical superiority of the PREZISTA/ritonavir regimen over the lopinavir/ritonavir regimen was demonstrated for both ITT and OP populations.

14.3 Treatment-Experienced Adult Subjects

TMC114-C229

TMC114-C229 is a randomized, open-label trial comparing PREZISTA/ritonavir 800/100 mg once daily to PREZISTA/ritonavir 600/100 mg twice daily in treatment-experienced HIV-1-

infected patients with screening genotype resistance test showing no darunavir resistance associated substitutions (i.e. V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, L89V) and a screening viral load of greater than 1,000 HIV-1 RNA copies/mL. Both arms used an optimized background regimen consisting of greater than or equal to 2 NRTIs selected by the investigator.

HIV-1-infected subjects who were eligible for this trial 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 less than 50 copies/mL. Analyses included 590 subjects who had completed 48 weeks of treatment or discontinued earlier.

Table 21 compares the demographic and baseline characteristics between subjects in the PREZISTA/ritonavir 800/100 mg once daily arm and subjects in the PREZISTA/ritonavir 600/100 mg twice daily arm in trial TMC114-C229. No imbalances between the 2 arms were noted.

Table 21: Demographic and Baseline Characteristics of Subjects in Trial TMC114-C229

	PREZISTA/ritonavir 800/100 mg once daily + OBR N=294	**PREZISTA/ritonavir 600/100 mg twice daily + OBR N=296**
Demographic characteristics		
Median age (years) (range, years)	40 (18-70)	40 (18-77)
Sex		
Male	61%	67%
Female	39%	33%
Race		
White	35%	37%
Black	28%	24%
Hispanic	16%	20%
Asian	16%	14%
Baseline characteristics		
Mean baseline plasma HIV-1 RNA (log_{10} copies/mL)	4.19	4.13
Median baseline CD4+ cell count (cells/mm^3) (range, cells/mm^3)	219 (24-1306)	236 (44-864)
Percentage of patients with baseline viral load ≥100,000 copies/mL	13%	11%
Percentage of patients with baseline CD4+ cell count <200 cells/mm^3	43%	39%
Median darunavir fold change (range)[a]	0.50 (0.1-1.8)	0.50 (0.1-1.9)
Median number of resistance-associated[b]:		
PI mutations	3	4
NNRTI mutations	2	1
NRTI mutations	1	1
Percentage of subjects susceptible to all available PIs at baseline	88%	86%
Percentage of subjects with number of baseline primary protease inhibitor mutations[b]:		
0	84%	84%
1	8%	9%

2	5%	4%
≥3	3%	2%
Median number of ARVs previously used[c]:		
NRTIs	3	3
NNRTIs	1	1
PIs (excluding low-dose ritonavir)	1	1

OBR=optimized background regimen

[a] Based on phenotype (Antivirogram®).

[b] Johnson VA, Brun-Vézinet F, Clotet B, et al. Update of the drug resistance mutations in HIV-1: December 2008. Top HIV Med 2008; 16(5): 138-145.

[c] Only counting ARVs, excluding low-dose ritonavir.

Week 48 outcomes for subjects on PREZISTA/ritonavir 800/100 mg once daily from trial TMC114-C229 are shown in Table 22.

Table 22: Virologic Outcome of Randomized Treatment of Trial TMC114-C229 at 48 Weeks

	PREZISTA/ritonavir 800/100 mg once daily + OBR N=294	**PREZISTA/ritonavir 600/100 mg twice daily + OBR N=296**
Virologic success HIV-1 RNA <50 copies/mL	69%	69%
Virologic failure[a]	26%	23%
No virologic data at Week 48 window[b]		
Reasons		
Discontinued trial due to adverse event or death[c]	3%	4%
Discontinued trial for other reasons[d]	2%	3%
Missing data during window[b] but on trial	0%	<1%

N = total number of subjects with data; OBR=optimized background regimen

[a] Includes patients who discontinued prior to Week 48 for lack or loss of efficacy, patients who are ≥50 copies in the 48-week window, patients who had a change in their background regimen that was not permitted in the protocol (provided the switch occurred before the earliest onset of an AE leading to permanent stop of trial medication) and patients who discontinued for reasons other than AEs/death and lack or loss of efficacy (provided their last available viral load was detectable (HIV RNA ≥50 copies/mL).

[b] Window 42-54 Weeks

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

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

The mean increase from baseline in CD4+ cell counts was comparable for both treatment arms (108 cells/mm^3 and 112 cells/mm^3 in the PREZISTA/ritonavir 800/100 mg once daily arm and the PREZISTA/ritonavir 600/100 mg twice daily arm, respectively).

TMC114-C214

TMC114-C214 is a randomized, controlled, open-label Phase 3 trial comparing PREZISTA/ritonavir 600/100 mg twice daily versus lopinavir/ritonavir 400/100 mg twice daily in antiretroviral treatment-experienced, lopinavir/ritonavir-naïve HIV-1-infected adult subjects. Both arms used an optimized background regimen 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 greater than 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 less than

400 copies/mL. Analyses included 595 subjects in trial TMC114-C214 who had completed 96 weeks of treatment or discontinued earlier.

Demographics and baseline characteristics were balanced between the PREZISTA/ritonavir arm and the lopinavir/ritonavir arm (see Table 23). Table 23 compares the demographic and baseline characteristics between subjects in the PREZISTA/ritonavir 600/100 mg twice daily arm and subjects in the lopinavir/ritonavir 400/100 mg twice daily arm in trial TMC114-C214.

Table 23: Demographic and Baseline Characteristics of Subjects in Trial TMC114-C214

	PREZISTA/ritonavir 600/100 mg twice daily + OBR N=298	**lopinavir/ritonavir 400/100 mg twice daily + OBR N=297**
Demographic characteristics		
Median age (years) (range, years)	40 (18-68)	41 (22-76)
Sex		
Male	77%	81%
Female	23%	19%
Race		
White	54%	57%
Black	18%	17%
Hispanic	15%	15%
Asian	9%	9%
Baseline characteristics		
Mean baseline plasma HIV-1 RNA (log_{10} copies/mL)	4.33	4.28
Median baseline CD4+ cell count (cells/mm^3) (range, cells/mm^3)	235 (3-831)	230 (2-1096)
Percentage of patients with baseline viral load ≥100,000 copies/mL	19%	17%
Percentage of patients with baseline CD4+ cell count <200 cells/mm^3	40%	40%
Median darunavir fold change (range)	0.60 (0.10-37.40)	0.60 (0.1-43.8)
Median lopinavir fold change (range)	0.70 (0.40-74.40)	0.80 (0.30-74.50)
Median number of resistance-associated[a]:		
PI mutations	4	4
NNRTI mutations	1	1
NRTI mutations	2	2
Percentage of subjects with number of baseline primary protease inhibitor mutations[a]:		
≤1	78%	80%
2	8%	9%
≥3	13%	11%
Median number of ARVs previously used[b]:		
NRTIs	4	4
NNRTIs	1	1
PIs (excluding low-dose ritonavir)	1	1
Percentage of subjects resistant[c] to all available[d] PIs at baseline, excluding darunavir	2%	3%

OBR=optimized background regimen

[a] 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.

[b] Only counting ARVs, excluding low-dose ritonavir.

[c] Based on phenotype (Antivirogram®).

[d] Commercially available PIs at the time of trial enrollment.

Week 96 outcomes for subjects on PREZISTA/ritonavir 600/100 mg twice daily from trial TMC114-C214 are shown in Table 24.

Table 24: Virologic Outcome of Randomized Treatment of Trial TMC114-C214 at 96 Weeks

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

N = total number of subjects with data; OBR=optimized background regimen

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

[b] Window 90-102 Weeks.

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

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

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

TMC114-C213 and TMC114-C202

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

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

The virologic response rate was evaluated in subjects receiving PREZISTA/ritonavir plus an OBR versus a control group receiving an investigator-selected PI(s) regimen plus an OBR. Prior to randomization, PI(s) and OBR were selected by the investigator based on genotypic resistance testing and prior ARV history. The OBR consisted of at least 2 NRTIs with or without enfuvirtide. Selected PI(s) in the control arm included: lopinavir in 36%, (fos)amprenavir in 34%, saquinavir in 35% and atazanavir in 17%; 98% of control subjects received a ritonavir boosted PI regimen out of which 23% of control subjects used dual-boosted PIs. Approximately 47% of all subjects

used enfuvirtide, and 35% of the use was in subjects who were ENF-naïve. Virologic response was defined as a decrease in plasma HIV-1 RNA viral load of at least 1 $\log_{10}$ versus baseline.

In the pooled analysis for TMC114-C213 and TMC114-C202, demographics and baseline characteristics were balanced between the PREZISTA/ritonavir arm and the comparator PI arm (see Table 25). Table 25 compares the demographic and baseline characteristics between subjects in the PREZISTA/ritonavir 600/100 mg twice daily arm and subjects in the comparator PI arm in the pooled analysis of trials TMC114-C213 and TMC114-C202.

Table 25: Demographic and Baseline Characteristics of Subjects in the Trials TMC114-C213 and TMC114-C202 (Pooled Analysis)

	PREZISTA/ritonavir 600/100 mg twice daily + OBR N=131	**Comparator PI(s) + OBR N=124**
Demographic characteristics		
Median age (years) (range, years)	43 (27-73)	44 (25-65)
Sex		
Male	89%	88%
Female	11%	12%
Race		
White	81%	73%
Black	10%	15%
Hispanic	7%	8%
Baseline characteristics		
Mean baseline plasma HIV-1 RNA ($\log_{10}$ copies/mL)	4.61	4.49
Median baseline CD4+ cell count (cells/mm^3) (range, cells/mm^3)	153 (3-776)	163 (3-1274)
Percentage of patients with baseline viral load >100,000 copies/mL	24%	29%
Percentage of patients with baseline CD4+ cell count <200 cells/mm^3	67%	58%
Median darunavir fold change	4.3	3.3
Median number of resistance-associated[a]:		
PI mutations	12	12
NNRTI mutations	1	1
NRTI mutations	5	5
Percentage of subjects with number of baseline primary protease inhibitor mutations[a]:		
≤1	8%	9%
2	22%	21%
≥3	70%	70%
Median number of ARVs previously used[b]:		
NRTIs	6	6
NNRTIs	1	1
PIs (excluding low-dose ritonavir)	5	5
Percentage of subjects resistant[b] to all available[c] PIs at baseline, excluding tipranavir and darunavir	63%	61%
Percentage of subjects with prior use of enfuvirtide	20%	17%

OBR=optimized background regimen

[a] 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.

[b] Based on phenotype (Antivirogram®).

[c] Commercially available PIs at the time of trial enrollment.

Week 96 outcomes for subjects on the recommended dose PREZISTA/ritonavir 600/100 mg twice daily from the pooled trials TMC114-C213 and TMC114-C202 are shown in Table 26.

Table 26: Outcomes of Randomized Treatment Through Week 96 of the Trials TMC114-C213 and TMC114-C202 (Pooled Analysis)

	Randomized trials TMC114-C213 and TMC114-C202	
	PREZISTA/ritonavir 600/100 mg twice daily + OBR N=131	**Comparator PI(s) + 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[a]	8%	53%
Rebounder[b]	17%	19%
Never suppressed[c]	4%	8%
Death or discontinuation due to adverse events	9%	3%
Discontinuation due to other reasons	5%	7%

OBR=optimized background regimen

[a] Subjects who did not achieve at least a confirmed 0.5 $\log_{10}$ HIV-1 RNA drop from baseline at Week 12.

[b] 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.

[c] Subjects who never reached a confirmed 1 $\log_{10}$ drop in viral load before Week 96.

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

14.4 Pediatric Patients

The pharmacokinetic profile, safety and antiviral activity of PREZISTA/ritonavir were evaluated in 3 randomized, open-label, multicenter studies.

TMC114-C212

Treatment-experienced pediatric subjects between the ages of 6 and less than 18 years and weighing at least 20 kg were stratified according to their weight (greater than or equal to 20 kg to less than 30 kg, greater than or equal to 30 kg to less than 40 kg, greater than or equal to 40 kg) and received PREZISTA tablets with either ritonavir capsules or oral solution plus background therapy consisting of at least two non-protease inhibitor antiretroviral drugs. Eighty patients were randomized and received at least one dose of PREZISTA/ritonavir. Pediatric subjects who were at risk of discontinuing therapy due to intolerance of ritonavir oral solution (e.g., taste aversion) were

allowed to switch to the capsule formulation. Of the 44 pediatric subjects taking ritonavir oral solution, 23 subjects switched to the 100 mg capsule formulation and exceeded the weight-based ritonavir dose without changes in observed safety.

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

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

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

TMC114-C228

Treatment-experienced pediatric subjects between the ages of 3 and less than 6 years and weighing greater than or equal to 10 kg to less than 20 kg received PREZISTA oral suspension with ritonavir oral solution plus background therapy consisting of at least two active non-protease inhibitor antiretroviral drugs. Twenty-one subjects received at least one dose of PREZISTA/ritonavir.

The 21 subjects had a median age of 4.4 years (range 3 to less than 6 years), and were 48% male, 57% Black, 29%, Caucasian and 14% other. The mean baseline plasma HIV-1 was 4.34 $\log_{10}$ copies/mL, the median baseline CD4+ cell count was 927 × 10^6 cells/L (range: 209 to 2,429 × 10^6 cells/L) and the median baseline CD4+ percentage was 27.7% (range: 15.6% to 51.1%). Overall, 24% of subjects had a baseline plasma HIV-1 RNA greater than or equal to 100,000 copies/mL. All subjects had used greater than or equal to 2 NRTIs, 62% of subjects had used greater than or equal to 1 NNRTI and 76% had previously used at least one HIV PI.

Twenty subjects (95%) completed the 48 week period. One subject prematurely discontinued treatment due to vomiting assessed as related to ritonavir.

The proportion of subjects with HIV-1 RNA less than 50 copies/mL at Week 48 was 71%. The mean increase in CD4+ percentage from baseline was 4%. The mean change in CD4+ cell count from baseline was 187 × 10^6 cells/L.

TMC114-C230

Treatment-naïve pediatric subjects between the ages of 12 and less than 18 years and weighing at least 40 kg received the adult recommended dose of PREZISTA/ritonavir 800/100 mg once daily plus background therapy consisting of at least two non-protease inhibitor antiretroviral drugs.

The 12 randomized pediatric subjects had a median age of 14.4 years (range 12.6 to 17.3 years), and were 33.3% male, 58.3% Caucasian and 41.7% Black. The mean baseline plasma HIV-1 RNA was 4.72 $\log_{10}$ copies/mL, and the median baseline CD4+ cell count was 282 cells/mm^3 (range: 204 to 515 cells/mm^3). Overall, 41.7% of pediatric subjects had baseline plasma HIV-1 RNA ≥100,000 copies/mL.

All subjects completed the 48 week treatment period.

The proportion of subjects with HIV-1 RNA less than 50 copies/mL and less than 400 copies/mL was 83.3% and 91.7%, respectively. The mean increase in CD4+ cell count from baseline was 221×10^6 cells/L.

16 HOW SUPPLIED/STORAGE AND HANDLING

PREZISTA® (darunavir) 100 mg per mL oral suspension is a white to off-white opaque liquid supplied in amber-colored multiple-dose bottles containing 100 mg of darunavir per mL packaged with a 6 mL oral dosing syringe with 0.2 mL gradations.

PREZISTA® (darunavir) 75 mg tablets are supplied as white, caplet-shaped, film-coated tablets debossed with “75” on one side and “TMC” on the other side.

PREZISTA® (darunavir) 150 mg tablets are supplied as white, oval-shaped, film-coated tablets debossed with “150” on one side and “TMC” on the other side.

PREZISTA® (darunavir) 600 mg tablets are supplied as orange, oval-shaped, film-coated tablets debossed with “600MG” on one side and “TMC” on the other side.

PREZISTA® (darunavir) 800 mg tablets are supplied as dark red, oval-shaped, film-coated tablets debossed with “800” on one side and “T” on the other side.

PREZISTA is packaged in bottles in the following configuration:

- 100 mg/mL oral suspension – 200 mL bottles (NDC 59676-565-01)
- 75 mg tablets — bottles of 480 (NDC 59676-563-01)
- 150 mg tablets — bottles of 240 (NDC 59676-564-01)
- 600 mg tablets — bottles of 60 (NDC 59676-562-01)
- 800 mg tablets — bottles of 30 (NDC 59676-566-30)

Storage

PREZISTA Oral Suspension

- Store at 25°C (77°F); with excursions permitted to 15°-30°C (59°-86°F).
- Do not refrigerate or freeze. Avoid exposure to excessive heat.
- Store in the original container.

- Shake well before each usage.

PREZISTA Tablets

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

Keep PREZISTA out of reach of children.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instruction for Use).

Instructions for Use

Advise patients to take PREZISTA and ritonavir with food every day on a regular dosing schedule, as missed doses can result in development of resistance. PREZISTA must always be used with ritonavir in combination with other antiretroviral drugs. Advise patients not to alter the dose of either PREZISTA or ritonavir, discontinue ritonavir, or discontinue therapy with PREZISTA without consulting their physician *[see Dosage and Administration (2)]*.

Hepatotoxicity

Inform patients that drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported with PREZISTA co-administered with 100 mg of ritonavir. Advise patients about the signs and symptoms of liver problems *[see Warnings and Precautions (5.2)]*.

Severe Skin Reactions

Inform patients that skin reactions ranging from mild to severe, including Stevens-Johnson Syndrome, drug rash with eosinophilia and systemic symptoms, and toxic epidermal necrolysis, have been reported with PREZISTA co-administered with 100 mg of ritonavir. Advise patients to discontinue PREZISTA/ritonavir immediately if signs or symptoms of severe skin reactions develop. These can include but are not limited to severe rash or rash accompanied with fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis and/or eosinophilia *[see Warnings and Precautions (5.3)]*.

Drug Interactions

PREZISTA/ritonavir may interact with many drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including St. John's wort *[see Contraindications (4), Warnings and Precautions (5.4, 5.5) and Drug Interactions (7)]*.

Contraception

Instruct patients receiving combined hormonal contraception or the progestin only pill to use an effective alternative (non-hormonal) contraceptive method or add a barrier method during therapy with PREZISTA/ritonavir because hormonal levels may decrease *[see Drug Interactions (7.3) and Use in Specific Populations (8.3)]*.

Fat Redistribution

Inform patients that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy, including PREZISTA/ritonavir, and that the cause and long-term health effects of these conditions are not known at this time *[see Warnings and Precautions (5.7)]*.

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any symptoms of infection, as in some patients with advanced HIV infection (AIDS), signs and symptoms of inflammation from previous infections may occur soon after anti-HIV treatment is started *[see Warnings and Precautions (5.8)]*.

Pregnancy Registry

Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes of pregnant women exposed to PREZISTA *[see Use in Specific Populations (8.1)]*.

Lactation

Instruct women with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in breast milk *[see Use in Specific Populations (8.2)]*.

Product of Ireland

Manufactured by:
PREZISTA oral suspension
Janssen Pharmaceutica, NV
Beerse, Belgium

PREZISTA tablets
Janssen Ortho LLC
Gurabo
PR 00778

Or

Janssen Cilag SpA
Latina
IT

Manufactured for:
Janssen Products, LP
Horsham PA 19044

PREZISTA® is a registered trademark of Janssen Pharmaceuticals.

PATIENT INFORMATION

PREZISTA® (pre-ZIS-ta)
(darunavir)
oral suspension

PREZISTA® (pre-ZIS-ta)
(darunavir)
tablet

Read this Patient Information before you start taking PREZISTA and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Also read the Patient Information leaflet for ritonavir.

What is the most important information I should know about PREZISTA?

- **Ask your healthcare provider or pharmacist about medicines that should not be taken with PREZISTA. For more information, see "Who should not take PREZISTA?" and "What should I tell my healthcare provider before taking PREZISTA?"**
- **PREZISTA may cause liver problems.** Some people taking PREZISTA in combination with ritonavir have developed liver problems, which may be life-threatening. Your healthcare provider should do blood tests before and during your PREZISTA and ritonavir combination treatment. If you have chronic hepatitis B or C infection, your healthcare provider should check your blood tests more often because you have an increased chance of developing liver problems. Tell your healthcare provider if you have any of the below signs and symptoms of liver problems.
  - dark (tea colored) urine
  - yellowing of your skin or whites of your eyes
  - pale colored stools (bowel movements)
  - nausea
  - vomiting
  - pain or tenderness on your right side below your ribs
  - loss of appetite
  - tiredness
- **PREZISTA may cause severe or life-threatening skin reactions or rash.** Sometimes these skin reactions and skin rashes can become severe and require treatment in a hospital. Tell your healthcare provider right away if you develop a rash. **Stop** taking PREZISTA and ritonavir combination treatment and tell your healthcare provider right away if you have any skin changes with symptoms below:
  - fever
  - tiredness
  - muscle or joint pain
  - blisters or skin lesions
  - mouth sores or ulcers
  - red or inflamed eyes, like "pink eye" (conjunctivitis)

Rash occurred more often in people taking PREZISTA and raltegravir together than with either drug separately, but was generally mild.

See **"What are the possible side effects of PREZISTA?"** for more information about side effects.

What is PREZISTA?

PREZISTA is a prescription HIV-1 (Human Immunodeficiency Virus-type 1) medicine used with ritonavir and other antiretroviral medicines to treat HIV-1 infection in adults and children 3 years of age and older. HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

PREZISTA should not be used in children under 3 years of age.

When used with other antiretroviral medicines to treat HIV-1 infection, PREZISTA may help:

- reduce the amount of HIV-1 in your blood. This is called "viral load".
- increase the number of CD4+ (T) cells in your blood that help fight off other infections.

Reducing the amount of HIV-1 and increasing the CD4+ (T) cells in your blood may improve your immune system. This may reduce your risk of death or getting infections that can happen when your immune system is weak (opportunistic infections).

PREZISTA does not cure HIV-1 infection or AIDS. You must keep taking HIV-1 medicines to control HIV-1 infection and decrease HIV-related illnesses.

Avoid doing things that can spread HIV-1 infection to others:

- Do not share or re-use needles or other injection equipment.
- Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.
- Do not have any kind of sex without protection. Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.

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

Who should not take PREZISTA?

Do not take PREZISTA with any medicine that contains:

- alfuzosin
- colchicine, if you have liver or kidney problems
- dronedarone
- elbasvir and grazoprevir
- ergot-containing medicines:
  - dihydroergotamine
  - ergotamine tartrate
  - methylergonovine
- ivabradine
- lomitapide
- lovastatin
- lurasidone
- midazolam, when taken by mouth
- naloxegol
- pimozide
- ranolazine
- rifampin
- sildenafil, when used for the treatment of pulmonary arterial hypertension (PAH)
- simvastatin
- St. John's wort (*Hypericum perforatum*)
- triazolam

Serious problems can happen if you or your child take any of these medicines with PREZISTA. This is not a complete list of medicines. Therefore, tell your healthcare provider about **all** medicines you take.

What should I tell my healthcare provider before taking PREZISTA?

Before taking PREZISTA, tell your healthcare provider if you:

- have liver problems, including hepatitis B or hepatitis C
- are allergic to sulfa medicines
- have high blood sugar (diabetes)
- have hemophilia
- have any other medical conditions
- are pregnant or plan to become pregnant. Tell your healthcare provider if you become pregnant while taking PREZISTA.
  - **Pregnancy Registry**: There is a pregnancy registry for women who take antiretroviral medicines during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk to your healthcare provider about how you can take part in this registry.
- are breastfeeding or plan to breastfeed. Do not breastfeed if you take PREZISTA.
  - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
  - It is not known if PREZISTA can pass into your breast milk.
  - Talk to your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, topical creams, vitamins, and herbal supplements. Some medicines interact with PREZISTA. **Keep a list of your medicines to show your healthcare provider and pharmacist.**

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with PREZISTA.
- **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take PREZISTA with other medicines.

How should I take PREZISTA?

- Take PREZISTA exactly as your healthcare provider tells you.
- You must take ritonavir at the same time as PREZISTA.
- Do not change your dose or stop treatment with PREZISTA without talking to your healthcare provider.
- Take PREZISTA and ritonavir with food.
- If you have difficulty swallowing PREZISTA tablets, PREZISTA oral suspension is also available. Your healthcare provider will help decide whether PREZISTA tablets or oral suspension is right for you.
- If your child is taking PREZISTA, your child's healthcare provider will decide the right dose based on your child's weight. Your child's healthcare provider will tell you how much PREZISTA (tablets or oral suspension) and how much ritonavir (capsules, tablets or solution) your child should take. Your child should take PREZISTA with

ritonavir with food. If your child does not tolerate ritonavir oral solution, ask your child's healthcare provider for advice.

- PREZISTA oral suspension should be given with the supplied oral dosing syringe. Shake the suspension well before each use. **See the "Instructions for Use" that come with PREZISTA oral suspension for information about the right way to prepare and take a dose.**
- It is important that you do not miss or skip doses of PREZISTA during treatment.
- If you take too much PREZISTA, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of PREZISTA?

PREZISTA may cause serious side effects, including:

- See "**What is the most important information I should know about PREZISTA?**"
- **Diabetes and high blood sugar (hyperglycemia).** Some people who take protease inhibitors including PREZISTA can get high blood sugar, develop diabetes, or your diabetes can get worse. Tell your healthcare provider if you notice an increase in thirst or urinate often while taking PREZISTA.
- **Changes in body fat** can happen in people who take HIV-1 medicines. The changes may include an increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the middle of your body (trunk). 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.
- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having new symptoms after starting your HIV-1 medicine.
- **Increased bleeding for hemophiliacs.** Some people with hemophilia have increased bleeding with protease inhibitors including PREZISTA.

The most common side effects of PREZISTA include:

- diarrhea
- nausea
- rash
- headache
- stomach-area (abdominal) pain
- vomiting

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of PREZISTA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store PREZISTA?

- Store PREZISTA oral suspension and tablets at room temperature 77°F (25°C).
- Do not refrigerate or freeze PREZISTA oral suspension.
- Keep PREZISTA oral suspension away from high heat.
- PREZISTA oral suspension should be stored in the original container.

Keep PREZISTA and all medicines out of the reach of children.

General information about the safe and effective use of PREZISTA.

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

This leaflet summarizes the most important information about PREZISTA. If you would like more information, talk to your healthcare provider. You can ask your healthcare provider or pharmacist for information about PREZISTA that is written for health professionals. For more information, call 1-800-526-7736.

What are the ingredients in PREZISTA?

Active ingredient: darunavir

Inactive ingredients:

PREZISTA oral suspension: citric acid monohydrate, hydrochloric acid (for pH adjustment), hydroxypropyl cellulose, masking flavor, methylparaben sodium, microcrystalline cellulose, purified water, sodium carboxymethylcellulose, strawberry cream flavor, and sucralose.

PREZISTA 75 mg and 150 mg tablets: colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose. The film coating contains: OPADRY® White (polyethylene glycol 3350, polyvinyl alcohol-partially hydrolyzed, talc, titanium dioxide).

PREZISTA 600 mg tablets: colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose. The film coating contains: OPADRY® Orange (FD&C Yellow No. 6, polyethylene glycol 3350, polyvinyl alcohol-partially hydrolyzed, talc, titanium dioxide).

PREZISTA 800 mg tablets: colloidal silicon dioxide, crospovidone, magnesium stearate, microcrystalline cellulose, hypromellose. The film coating contains: OPADRY® Dark Red (iron oxide red, polyethylene glycol 3350, polyvinyl alcohol-partially hydrolyzed, talc, titanium dioxide).

Product of Ireland
Manufactured by: PREZISTA oral suspension, Janssen Pharmaceutica NV, Beerse, Belgium
PREZISTA tablets, Janssen Ortho LLC, Gurabo, PR 00778 or Janssen Cilag SpA, Latina, IT
Manufactured for: Janssen Products, LP, Horsham PA 19044
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This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 10/2022