*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

	Formulation and Recommended Dosing	
Baseline Resistance	**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: <u>Direct Oral Anticoagulants (DOACs)</u> 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 Other: trazodone	↑ amitriptyline ↑ desipramine ↑ imipramine ↑ nortriptyline ↑ trazodone	Use a lower dose of the tricyclic antidepressants and trazodone due to potential increased adverse events such as nausea, dizziness, hypotension and syncope.
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	<u>Initiation of PREZISTA with ritonavir in patients taking quetiapine:</u> 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. <u>Initiation of quetiapine in patients taking PREZISTA with ritonavir:</u> 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.
<u>Other antiarrhythmics</u> 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	<u>Co-administration of bosentan in patients on PREZISTA/ritonavir:</u> 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. <u>Co-administration of PREZISTA/ritonavir in patients on bosentan:</u> 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): <u>Direct-Acting Antivirals:</u> 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. <u>Use of PDE-5 inhibitors for erectile dysfunction:</u> 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)]*.

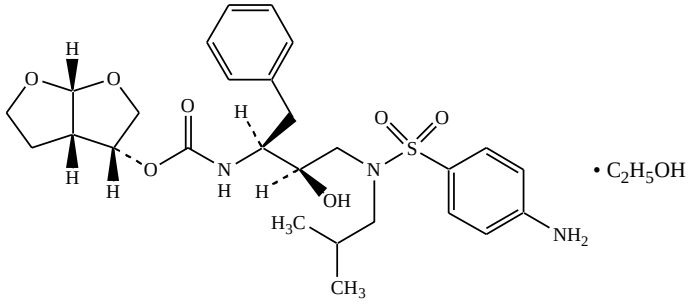
10 OVERDOSAGE

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}

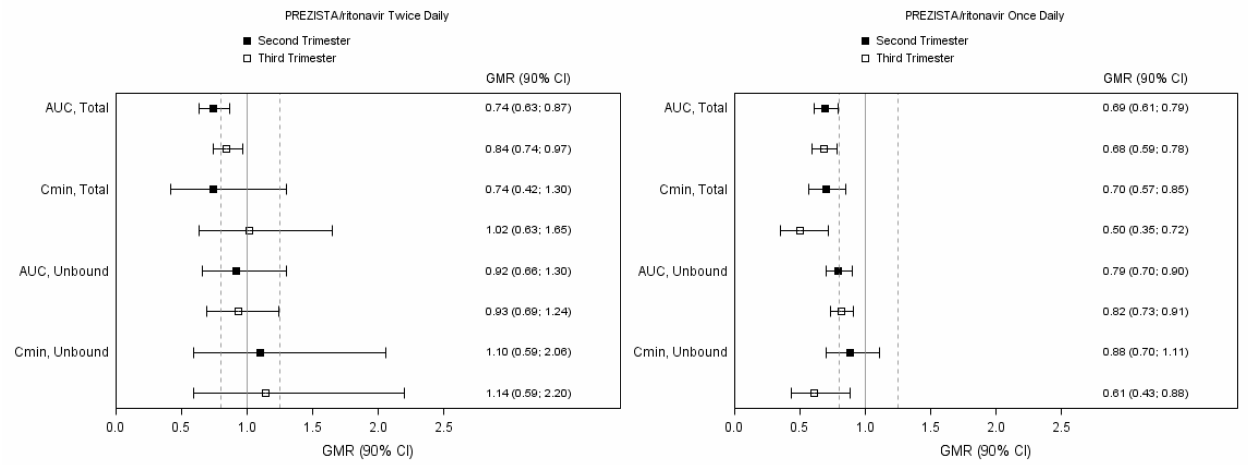
[b] AUC_{24h} is calculated as AUC_{12h}*2.

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

	Dose/Schedule				**LS Mean ratio (90% CI) of darunavir Pharmacokinetic parameters with/without co-administered drug 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]	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)