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

PREZISTA (darunavir) Tablet, Film Coated for Oral use

Initial U.S. Approval – 2006

----------RECENT MAJOR CHANGES----------
- Dosage and Administration
  - Adult Patients (2.1) 12/2010
- Contraindications (4) 04/2010
- Warnings and Precautions
  - Severe Skin Reactions (5.3) 01/2010

----------INDICATIONS AND USAGE----------
PREZISTA is a human immunodeficiency virus (HIV-1) protease inhibitor indicated for the treatment of HIV-1 infection in adult patients. PREZISTA is also indicated for the treatment of HIV-1 infection in pediatric patients 6 years of age and older. PREZISTA must be co-administered with ritonavir (PREZISTA/ritonavir) and with other antiretroviral agents. (1)

----------DOSAGE AND ADMINISTRATION----------
- Treatment-naïve adult patients and treatment-experienced adult patients with no darunavir resistance associated substitutions: 800 mg (two 400 mg tablets) taken with ritonavir 100 mg once daily and with food. (2.1)
- 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. (2.1)
- Pediatric patients (6 to less than 18 years of age and weighing at least 44 lbs (20 kg)): dosage of PREZISTA and ritonavir is based on body weight and should not exceed the treatment-experienced adult dose. Do not use once daily dosing in pediatric patients. PREZISTA tablets should be taken with ritonavir twice daily and with food. (2.2)
- PREZISTA/ritonavir is not recommended for use in patients with severe hepatic impairment. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
75 mg tablets, 150 mg tablets, 400 mg tablets, and 600 mg tablets (3)

----------CONTRAINDICATIONS----------
Co-administration with alfuzosin, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, pimozide, oral midazolam, triazolam, St. Johns Wort, lovastatin, simvastatin, rifampin and sildenafil (for treatment of pulmonary arterial hypertension). (4)
- Due to the need for co-administration of PREZISTA with 100 mg of ritonavir, please refer to ritonavir prescribing information for a description of ritonavir contraindications.

----------WARNINGS AND PRECAUTIONS----------
- Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported with PREZISTA/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, 6)
- Skin reactions ranging from mild to severe, including Stevens-Johnson Syndrome and toxic epidermal necrolysis, have been reported. Discontinue treatment if severe reaction develops. (5.3, 6)
- Use with caution in patients with a known sulfonamide allergy. (5.4)
- Patients may develop new onset diabetes mellitus or hyperglycemia. Initiation or dose adjustments of insulin or oral hypoglycemic agents may be required. (5.6)
- Patients may develop redistribution/accumulation of body fat (5.7) or immune reconstitution syndrome. (5.8)
- Patients with hemophilia may develop increased bleeding events. (5.9)
- PREZISTA/ritonavir should not be used in pediatric patients below 3 years of age in view of toxicity and mortality observed in juvenile rats dosed with darunavir up to days 23 to 26 of age The safety and efficacy of PREZISTA/ritonavir in pediatric patients 3 to < 6 years of age have not been established. (5.11)

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

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

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

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

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

Revised: 12/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Adult Patients

PREZISTA®, co-administered with ritonavir (PREZISTA/ritonavir), and with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV-1) infection.

This indication is based on analyses of plasma HIV-1 RNA levels and CD4+ cell counts from 2 controlled Phase 3 trials of 48 weeks duration in antiretroviral treatment-naïve and treatment-experienced patients and 2 controlled Phase 2 trials of 96 weeks duration in clinically advanced, treatment-experienced adult patients.

1.2 Pediatric Patients

PREZISTA, co-administered with ritonavir (PREZISTA/ritonavir), and with other antiretroviral agents, is indicated for the treatment of HIV-1 infection in pediatric patients 6 years of age and older [*see Use in Specific Populations (8.4)*].

This indication is based on 24-week analyses of plasma HIV-1 RNA levels and CD4+ cell counts from an open-label Phase 2 trial in antiretroviral treatment-experienced pediatric patients 6 to < 18 years of age.

In treatment-experienced adult and pediatric patients, the following points should be considered when initiating therapy with PREZISTA/ritonavir:

- Treatment history and, when available, genotypic or phenotypic testing should guide the use of PREZISTA/ritonavir [*see Clinical Pharmacology (12.4)*].
- The use of other active agents with PREZISTA/ritonavir is associated with a greater likelihood of treatment response [*see Clinical Pharmacology (12.4) and Clinical Studies (14.3)*].

2 DOSAGE AND ADMINISTRATION

2.1 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.

Treatment-Naïve Adult Patients

The recommended oral dose of PREZISTA tablets is 800 mg (two 400 mg tablets) taken with ritonavir 100 mg once daily and with food.

Treatment-Experienced Adult Patients

Treatment-Experienced Adult Patients	
With no darunavir resistance associated substitutions*	With at least one darunavir resistance associated substitution*
800 mg PREZISTA once daily with ritonavir 100 mg once daily and with food	600 mg PREZISTA twice daily taken with ritonavir 100 mg twice daily and with food

* V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V and L89V

For antiretroviral treatment-experienced patients genotypic testing is recommended. However, when genotypic testing is not feasible, PREZISTA/ritonavir 600/100 mg twice daily dosing is recommended.

2.2 Pediatric Patients (age 6 to less than 18 years)

Do not use once daily dosing in pediatric patients.

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 treatment-experienced adults.

Before prescribing PREZISTA, children should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow a tablet, the use of PREZISTA tablets may not be appropriate.

The recommended dose of PREZISTA/ritonavir for pediatric patients (6 to less than 18 years of age and weighing at least 44 lbs (20 kg)) is based on body weight (see Table 1) and should not exceed the recommended treatment-experienced adult dose (PREZISTA/ritonavir 600/100 mg b.i.d.). PREZISTA tablets should be taken with ritonavir twice daily and with food.

Table 1: Recommended Dose for Pediatric Patients (6 to less than 18 years of age) for PREZISTA Tablets with ritonavir

Body Weight		Dose
(kg)	**(lbs)**	
Greater than or equal to 20 kg – less than 30 kg	Greater than or equal to 44 lbs – less than 66 lbs	375 mg PREZISTA/50 mg ritonavir twice daily
Greater than or equal to 30 kg – less than 40 kg	Greater than or equal to 66 lbs – less than 88 lbs	450 mg PREZISTA/60 mg ritonavir twice daily
Greater than or equal to 40 kg	Greater than or equal to 88 lbs	600 mg PREZISTA/100 mg ritonavir twice daily

The safety and efficacy of PREZISTA/ritonavir in pediatric patients 3 to less than 6 years of age have not been established.

Do not use PREZISTA/ritonavir in pediatric patients below 3 years of age [*see Warnings and Precautions (5.11) and Nonclinical Toxicology (13.2)*].

2.3 Patients with Hepatic Impairment

No dose adjustment is required in patients with mild or moderate hepatic impairment. No data are available regarding the use of PREZISTA/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

3.1 PREZISTA 75 mg Tablets

PREZISTA (darunavir) 75 mg tablets are supplied as white, caplet-shaped, film-coated tablets containing darunavir ethanolate equivalent to 75 mg of darunavir per tablet. Each tablet is debossed with “75” on one side and “TMC” on the other side.

3.2 PREZISTA 150 mg Tablets

PREZISTA (darunavir) 150 mg tablets are supplied as white, oval-shaped, film-coated tablets containing darunavir ethanolate equivalent to 150 mg of darunavir per tablet. Each tablet is debossed with “150” on one side and “TMC” on the other side.

3.3 PREZISTA 400 mg Tablets

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

3.4 PREZISTA 600 mg Tablets

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

4 CONTRAINDICATIONS

Co-administration of PREZISTA/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). These drugs and other contraindicated drugs (which may lead to reduced efficacy of darunavir) are listed in Table 2 [*also see Drug Interactions (7.3)*, Table 7].

Table 2: Drugs That Are Contraindicated With PREZISTA/ritonavir

Drug Class	Drugs Within Class That Are Contraindicated With PREZISTA/ritonavir	Clinical Comment
Alpha 1-adrenoreceptor antagonist	Alfuzosin	Potential for serious and/or life-threatening reactions such as hypotension.
Ergot Derivatives	Dihydroergotamine, Ergonovine, Ergotamine, Methylergonovine	Potential for serious and/or life-threatening events such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent	Cisapride	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Neuroleptic	Pimozide	Potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Sedative/hypnotics	Orally administered Midazolam, Triazolam	Triazolam and orally administered midazolam are extensively metabolized by CYP3A. Co-administration of triazolam or orally administered midazolam with PREZISTA/ritonavir may cause large increases in the concentrations of these benzodiazepines. Potential for serious and/or life-threatening events such as prolonged or increased sedation or respiratory depression.
Herbal Products	St. John's Wort (*Hypericum perforatum*)	Patients taking PREZISTA/ritonavir should not use products containing St. John's wort because co-administration may result in reduced plasma concentrations of darunavir. This may result in loss of therapeutic effect and development of resistance.

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