## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

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

Contraindications (4) 05/2015
Warnings and Precautions
- Risk of Serious Adverse Reactions due to Drug Interactions (5.5) 03/2015

### ----------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 3 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 (one 800 mg tablet) 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 (3 to less than 18 years of age and weighing at least 10 kg): dosage of PREZISTA and ritonavir is based on body weight and should not exceed the adult dose. PREZISTA should be taken with ritonavir and with food. (2.2)
- PREZISTA/ritonavir is not recommended for use in patients with severe hepatic impairment. (2.3)

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

- 100 mg/mL oral suspension (3)
- 75 mg tablets, 150 mg tablets, 600 mg tablets, and 800 mg tablets (3)

### ----------CONTRAINDICATIONS----------

- Co-administration with alfuzosin, cisapride, colchicine (in patients with renal and/or hepatic impairment), dronedarone, dihydroergotamine, ergotamine, lovastatin, methylergonovine, oral midazolam, pimozide, ranolazine, rifampin, sildenafil (for treatment of pulmonary arterial hypertension), simvastatin, St. John's Wort, and triazolam. (4)
- Due to the need for co-administration of PREZISTA with ritonavir, please refer to ritonavir prescribing information for a description of ritonavir contraindications. (4)

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

- Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported with PREZISTA/ritonavir. Monitor liver function before and during therapy, especially in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases. Post-marketing cases of liver injury, including some fatalities, have been reported. (5.2, 6)
- Skin reactions ranging from mild to severe, including Stevens-Johnson Syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms and acute generalized exanthematous pustulosis, have been reported. Discontinue treatment if severe reaction develops. (5.3, 6)
- Use with caution in patients with a known sulfonamide allergy. (5.4)
- The concomitant use of PREZISTA/ritonavir and certain other drugs may result in known or potentially significant drug interactions. Consult the full prescribing information prior to and during treatment for potential drug interactions. (5.5, 7.3)
- 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. (5.11)

### ----------ADVERSE REACTIONS----------

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

**To report SUSPECTED ADVERSE REACTIONS, contact Janssen Products, LP at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.***

### ----------DRUG INTERACTIONS----------

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

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

- Use during pregnancy only if the potential benefit justifies the potential risk. (8.1)
- 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: 05/2015**

**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 3 years of age and older [see *Use in Specific Populations (8.4)*].

The indication for treatment-experienced pediatric patients 3 to less than 18 years of age is based on analyses of plasma HIV-1 RNA levels and CD4+ cell counts from two open-label Phase 2 trials in antiretroviral treatment-experienced pediatric subjects (24-week analysis for one trial in patients 6 to less than 18 years of age; 48-week analysis for one trial in patients 3 to less than 6 years of age). The indication for treatment-naïve pediatric patients or antiretroviral treatment-experienced patients with no darunavir resistance associated substitutions is based on one open-label Phase 2 trial of 48 weeks duration in antiretroviral treatment-naïve subjects 12 to less than 18 years of age and pharmacokinetic modeling and simulation for patients 3 to less than 12 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 *Microbiology (12.4)*].
- The use of other active agents with PREZISTA/ritonavir is associated with a greater likelihood of treatment response [see *Microbiology (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.

Patients who have difficulty swallowing PREZISTA tablets can use the 100 mg/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/capsule or 1.25 mL of a 80 mg/mL ritonavir oral solution) once daily and with food. An 8 mL darunavir dose should be taken as two 4 mL administrations with the included oral dosing syringe.

### *Treatment-Experienced Adult Patients*

| **Table 1: Treatment-Experienced Adult Patients** | |
|---|---|
| With no darunavir resistance associated substitutions* | With at least one darunavir resistance associated substitution* |
| **Formulations: PREZISTA tablets or oral suspension (100 mg/mL) and ritonavir tablets/capsules (100 mg) or solution (80 mg/mL)** | |
| PREZISTA 800 mg (one 800 mg tablet) or 8 mL† (oral suspension) once daily with ritonavir 100 mg (one 100 mg tablet/capsule or 1.25 mL (oral solution) once daily and with food | PREZISTA 600 mg (e.g. one 600 mg tablet) or 6 mL (oral suspension) twice daily with ritonavir 100 mg (one 100 mg tablet/capsule or 1.25 mL (oral solution) twice daily and with food |

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

† An 8 mL darunavir dose should be taken as two 4 mL administrations with the included oral dosing syringe

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 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 the following:

*Twice daily dosing*

- Results from two trials in treatment-experienced pediatric subjects 3 to less 18 years of age demonstrating similar darunavir plasma exposures, virologic response rate and safety profile compared to treatment-experienced adults.

*Once daily dosing*

- Results from one trial in treatment-naïve pediatric subjects 12 to less than 18 years of age demonstrating similar darunavir plasma exposures, virologic response rate and safety profile compared to treatment-naïve adults.
- Results from population pharmacokinetic modeling and simulation in children 3 to less than 12 years of age predicting similar darunavir plasma exposures compared to treatment-naïve adults. Although no clinical trial was conducted to collect exposure-safety data, the predicted exposures from the once daily dosing is supported by exposures observed in a pediatric clinical trial where twice-daily dosing was administered.

*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***

| **Body weight (kg)** | **Formulation: PREZISTA oral suspension (100 mg/mL) and Ritonavir oral solution (80 mg/mL)** |
|---|---|
| | **Dose: once daily with food** |
| Greater than or equal to 10 kg to less than 11 kg | PREZISTA 3.6 mL‡ (350 mg) with ritonavir 0.8 mL (64 mg) |
| Greater than or equal to 11 kg to less than 12 kg | PREZISTA 4 mL‡ (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‡ (455 mg) with ritonavir 1 mL (80 mg) |
| Greater than or equal to 14 kg to less than 15 kg | PREZISTA 5 mL‡ (490 mg) with ritonavir 1.2 mL (96 mg) |

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

‡ 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:

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