



NDA 202895/S-01

**SUPPLEMENT APPROVAL**

Janssen Products, L.P.  
Attention: Charles Zezza, Ph.D.  
Director, Global Regulatory Affairs  
920 Route 202 S  
Raritan, NJ 08869

Dear Dr. Zezza:

Please refer to your Supplemental New Drug Application (sNDA) dated and received January 6, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Prezista<sup>®</sup> (darunavir), Oral suspension.

We acknowledge receipt of your amendments dated February 7, 2012 in response to our comments to your January 6, 2012 supplement submission, sent via e-mail on February 3, 2012.

We note that this submission also refers to your NDA 21976/S-022, a prior approval supplement (PAS)-labeling submission made in response to our Safety Labeling Change Notification dated October 19, 2011 and to your January 6, 2012 response submitted to NDA 21976/S-022 in response to our General Advice letter of December 12, 2011.

In addition, we refer to non-safety labeling changes in our October 19, 2011 letter sent to your NDA 21976 for all antiretroviral products based on recent studies demonstrating decreased transmission of HIV when HIV-infected patients or their uninfected partners take antiretroviral medication.

This supplemental new drug application provides for revisions to the labeling for Prezista<sup>®</sup> (darunavir) oral solution, consistent with our October 19 and December 12, 2011 letters and February 3, 2012 e-mail comments, as follows (additions are noted by underline and deletions are noted by ~~strikethrough~~).

1. The **RECENT MAJOR CHANGES** in the Highlights section of the labeling has been revised as follows:

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

- Indications and Usage
  - Pediatric Patients (1.2) 12/2011
- Dosage and Administration
  - Adult Patients (2.1) 12/2011

- Pediatric Patients (2.2) 12/2011
  - Warnings and Precautions
    - Severe Skin Reactions (5.3) 10/2011
    - Immune Reconstitution Syndrome (5.8) 02/2012
    - Pediatric Patients (5.11) 12/2011
2. The revision date has been changed from 12/2011 to 02/2012 throughout the label.
3. The **WARNINGS AND PRECAUTIONS/Immune Reconstitution Syndrome** subsection has been revised as follows:

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 responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections (such as Mycobacterium avium infection complex, cytomegalovirus, Pneumocystis jirovecii pneumonia (PCP), and/or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) 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 treatment.

4. The Table 9 in the **7.3 Established and Other Potentially Significant Drug Interactions** section of the package insert has been revised as follows:

<p align="center"><b>Table 9: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction</b></p> <p align="center">[See <i>Clinical Pharmacology</i> (12.3) for Magnitude of Interaction, Tables 12 and 13]</p>		
<b>Concomitant Drug Class: Drug Name</b>	<b>Effect on Concentration of Lopinavir or Concomitant Drug</b>	<b>Clinical Comment</b>
<i>Other Agents</i>		
<p><b><u>HMG-CoA Reductase Inhibitors:</u></b> <u>pravastatin</u> <u>atorvastatin</u> <u>rosuvastatin</u></p>	<p><u>↑ pravastatin</u> <u>↑ atorvastatin</u> <u>↑ rosuvastatin</u></p>	<p><u>Titrate atorvastatin, pravastatin or rosuvastatin dose carefully and use the lowest possible necessary dose while monitoring for safety. Caution should be used when the Do not exceed atorvastatin dose exceeds 20 mg/day of atorvastatin, pravastatin or rosuvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as fluvastatin in combination with PREZISTA/ritonavir.</u></p>

5. The **PATIENT COUNSELING INFORMATION/Information About Therapy with PREZISTA** sub-section has been revised as follows:

~~Patients should be informed that PREZISTA is not a cure for HIV infection. Patients should stay on continuous HIV therapy to control HIV infection and decrease HIV-related illnesses.~~

~~Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician while using PREZISTA. Patients should be advised to continue to practice safer sex and to use latex or polyurethane condoms to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions or blood. Patients should be advised never to share personal items that can have blood or body fluids on them, like toothbrushes and razor blades. Patients should be advised never to re-use or share needles. PREZISTA is not a cure for HIV-1 infection and patients may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. Patients should remain under the care of a physician when using PREZISTA.~~

~~Patients should be advised to avoid doing things that can spread HIV-1 infection to others.~~

- **Do not share needles or other injection equipment.**
- **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**
- **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with semen, vaginal secretions, or blood.
- **Do not breastfeed.** We do not know if PREZISTA can be passed to the baby through breast milk and whether it could harm the baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.

6. **Patient Information:**

- a. The “**Does PREZISTA cure HIV or AIDS?**” section has been revised as follows:

**Does PREZISTA cure HIV or AIDS? What is PREZISTA?**

~~**PREZISTA does not cure HIV infection or AIDS.** People taking PREZISTA may still develop infections or other conditions associated with HIV infection, including opportunistic infections (e.g., pneumonia and herpes virus infections).~~

~~Patients must stay on continuous HIV therapy to control infection and decrease HIV related illnesses.~~

~~Avoid doing things that can spread HIV-1 infection.~~

- ~~▪ **Do not share needles or other injection equipment.**~~
- ~~▪ **Do not share personal items that can have blood or body fluids on them, like toothbrushes and razor blades.**~~
- ~~▪ **Do not have any kind of sex without protection.** Always practice safe sex by using a latex or polyurethane condom to lower the chance of sexual contact with any body fluids such as semen, vaginal secretions, or blood. Never re-use or share needles.~~

~~Ask your healthcare provider if you have any questions on how to prevent passing HIV to other people. PREZISTA does not cure HIV infection or AIDS and you may continue to experience illnesses associated with HIV-1 infection, including opportunistic infections. You should remain under the care of a doctor when using PREZISTA.~~

Avoid doing things that can spread HIV-1 infection.

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

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

- b. The “**Does PREZISTA reduce the risk of passing HIV to others?**” section has been deleted.
- c. The sixth bulleted paragraph in the “**What should I tell my doctor before taking PREZISTA?/ PREZISTA may not be right for you. Before taking PREZISTA, tell your doctor or healthcare provider if you:**” section has not been revised as follows:
  - are breastfeeding or plan to breastfeed. ~~Do not breastfeed if you are taking PREZISTA. You should not breastfeed if you have HIV because of the chance of passing HIV to your baby. Talk with your healthcare provider about the best way to feed your baby. The Centers for Disease Control and Prevention (CDC) recommends that HIV-infected mothers not breastfeed to avoid the risk of passing HIV infection to your baby.~~ **Do not breastfeed. We do not know if PREZISTA can be passed to your baby in your breast milk and whether it could harm your baby. Also, mothers with HIV-1 should not breastfeed because HIV-1 can be passed to the baby in the breast milk.**

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

## **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

## **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

**REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kyong Hyon, Safety Regulatory Project Manager, at (301) 796-0734.

Sincerely,

*{See appended electronic signature page}*

Kendall A. Marcus, MD  
Deputy Director for Safety  
Division of Antiviral Products  
Office Antimicrobial Products  
Center for Drug Evaluation and Research

ENCLOSURE(S):  
Content of Labeling

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

Initial U.S. Approval – 2006

**RECENT MAJOR CHANGES**

- Indications and Usage
  - Pediatric Patients (1.2) 12/2011
- Dosage and Administration
  - Adult Patients (2.1) 12/2011
  - Pediatric Patients (2.2) 12/2011
- Warnings and Precautions
  - Severe Skin Reactions (5.3) 10/2011
  - Immune Reconstitution Syndrome (5.8) 02/2012
  - Pediatric Patients (5.11) 12/2011

**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 (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 (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 treatment-experienced adult dose. Do not use once daily dosing in pediatric patients. PREZISTA 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**

- 100 mg/mL oral suspension (3)
- 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. John's Wort, lovastatin, simvastatin, rifampin and sildenafil (for treatment of pulmonary arterial hypertension). (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 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. (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](http://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)
  - Pregnancy Registry available. (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: 02/2012**

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

KENDALL A MARCUS  
02/17/2012