JANSSEN-ORTHO

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A DIVISION OF | UNE DIVISION DE JANSSEN-ORTHO INC.

APPROVAL OF
PREZISTA* (darunavir)
WITH CONDITIONS

August 10, 2006

Dear Health Professional(s),

Janssen-Ortho Inc. is pleased to announce that Health Canada has granted a Notice of Compliance with Conditions (NOC/c) for PREZISTA (darunavir/TMC114) tablets, a protease inhibitor for the treatment of human immunodeficiency virus (HIV) infection. The issuance of a marketing authorization with conditions under the NOC/c policy reflects the promising nature of the clinical evidence in patients with this serious disease. Confirmatory Phase 3 study is underway.

PREZISTA, co-administered with 100 mg ritonavir and other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV) infection in adult patients who have failed prior antiretroviral therapy.

In deciding on a new regimen for patients who have failed an antiretroviral regimen, careful consideration should be given to the treatment history of the individual patient and the patterns of mutations associated with different drugs.

PREZISTA must be administered with low-dose ritonavir (RTV) to ensure its therapeutic effect. Failure to correctly co-administer PREZISTA with ritonavir will result in reduced plasma levels of PREZISTA that may be insufficient to achieve the desired antiviral effect.

Darunavir and ritonavir are both inhibitors of the CYP3A4 isoform. Co-administration of PREZISTA/RTV is contraindicated with drugs that are highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events.

Drugs That Are Contraindicated With PREZISTA/RTV

Drug Class	Drugs Within Class That Are Contraindicated With PREZISTA/RTV
Antiarrhythmics	amiodarone, bepridil, lidocaine (systemic), quinidine
Antihistamines	astemizole[1], terfenadine[1]
Ergot Derivatives	dihydroergotamine, ergonovine, ergotamine, methylergonovine
GI Motility Agent	cisapride[1]
Neuroleptic	pimozide
Sedative/hypnotics	midazolam, triazolam
[1] astemizole, terfenadine and cisapride are no longer marketed in Canada.	

Co-administration of darunavir and ritonavir with drugs primarily metabolized by CYP3A4 may result in increased plasma concentrations of such drugs, which could increase or prolong their therapeutic effect leading to potentially serious adverse events.

The approval of PREZISTA is based on week-24 analyses from two randomized, controlled Phase 2 clinical trials in treatment-experienced, HIV-1 infected patients, where PREZISTA/RTV showed a significantly greater reduction of plasma HIV RNA levels and greater increase in CD4+ cell counts when compared to a protease inhibitor (PI) regimen of choice, each given in combination with other antiretroviral drugs.

In the pooled analysis of the Phase 2 trials through 24 weeks of therapy, there was a statistically significantly higher proportion of patients in the PREZISTA/RTV 600/100 mg b.i.d. arm compared to the comparator PI arm with an HIV-1 RNA decrease of at least 1.0 $\log_{10}$ from baseline (70% vs. 21%, respectively), with HIV-1 RNA < 400 copies/mL (63% vs. 19%, respectively), and with HIV-1 RNA < 50 copies/mL (45% vs. 12%, respectively). Similarly, at Week 24, the mean changes in plasma HIV-1 RNA from baseline were -1.89 $\log_{10}$ copies/mL in the arm receiving PREZISTA/RTV 600/100 mg b.i.d. and -0.48 $\log_{10}$ copies/mL for the comparator PI arm. The mean increase from baseline in CD4+ cell counts was statistically significantly higher in the arm receiving PREZISTA/RTV 600/100 mg b.i.d. (92 x 10^6 cells/L) than in the comparator PI arm (17 x 10^6 cells/L).

The majority of the adverse events reported in patients receiving PREZISTA/RTV 600/100 mg b.i.d. were grade 1 - 2 in severity. The most common treatment-emergent drug-related grade 1 - 4 adverse events occurring in > 5% of patients, who initiated treatment with the recommended dose, were nausea, diarrhea and headache. The most commonly reported grade 3 or 4 adverse events were increased blood amylase (3.3%) and increased GGT (2.2%). All other grade 3 or 4 adverse events were reported in less than 2% of the patients.

Phase 3 clinical studies are underway to evaluate the clinical benefits of PREZISTA in treatment-naïve and less experienced patient populations. Patients should be advised about the conditional nature of the marketing authorization for PREZISTA.

PREZISTA is available in 300 mg tablets for oral use.

The recommended oral dose of PREZISTA tablets is 600 mg (two 300 mg tablets) twice daily (b.i.d.) taken with ritonavir 100 mg b.i.d. and with food. The type of food does not affect exposure to PREZISTA. Ritonavir (100 mg b.i.d.) is used as a pharmacokinetic enhancer of PREZISTA.

The Product Monograph is available to physicians and pharmacists upon request.

A Fact Sheet on the use of PREZISTA in the treatment of HIV infection is available to consumers on the Health Canada website.

Should you have medical enquiries regarding PREZISTA for the treatment of HIV infection, please contact our Medical Information Department at 1-800-567-3331, or e-mail to dsscan@joica.jnj.com.

Original signed by

Cathy Lau
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Any suspected adverse drug reactions can also be reported to:
Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Marketed Health Products Directorate
HEALTH CANADA
Address Locator: 0701C
OTTAWA, Ontario, K1A 0K9
Tel: (613) 957-0337 or Fax: (613) 957-0335
Toll free for consumers and health professionals:
Tel: 866 234-2345, Fax: 866 678-6789
cadrmp@hc-sc.gc.ca

The AR Reporting Form and the AR Guidelines can be found on the Health Canada web site or in *The Canadian Compendium of Pharmaceuticals and Specialties*.