Health Canada Endorsed Important Safety Information on PREZISTA* (darunavir)

May 12, 2008

Dear Healthcare Professional:

Subject: New safety information regarding PREZISTA* (darunavir) and hepatotoxicity

Tibotec, a division of Janssen-Ortho Inc. ("Tibotec"), in cooperation with Health Canada, would like to inform you of important new safety information regarding hepatotoxicity in association with the use of PREZISTA (darunavir). PREZISTA, co-administered with ritonavir (rtv) and other antiretroviral agents, is indicated for treatment of human immunodeficiency virus (HIV) infection in adult patients who have failed prior antiretroviral therapy.

Drug-induced hepatotoxicity has been reported in patients receiving PREZISTA therapy in combination with rtv during clinical trials and post-marketing use.

- Drug-induced hepatitis (e.g. acute hepatitis, cytolytic hepatitis) has been reported with PREZISTA/rtv. During the clinical development program (N=3063), hepatitis was reported in 0.5% of patients receiving combination therapy with PREZISTA/rtv.

- For the period from June 23, 2006 to December 23, 2007, 13 post market reports of suspected drug-induced hepatitis were received. Two cases had a fatal outcome. During that same period, 25 reports were received of other hepatic adverse events such as hepatic cirrhosis, hepatic failure, hepatitis B or C, jaundice, and hepatic neoplasm, fourteen of which were associated with a fatal outcome. The contribution of PREZISTA to these hepatic adverse events and deaths has not been established. These cases have generally occurred in patients with advanced HIV-1 disease taking multiple concomitant medications, having co-morbidities including hepatitis B or C co-infection or liver cirrhosis, and/or developing immune reconstitution syndrome.

- Patients with pre-existing liver dysfunction, including chronic active hepatitis B or C, have an increased risk of severe hepatic adverse events. PREZISTA/rtv is not recommended for use in patients with pre-existing severe hepatic impairment.

Appropriate laboratory testing should be conducted prior to initiating therapy with PREZISTA/rtv and patients should be monitored during treatment. Increased AST/ALT monitoring, especially during the first several months of PREZISTA/rtv, should be considered in patients with underlying chronic hepatitis (including hepatitis B or C virus co-infection) or cirrhosis, as well as in patients with elevated liver enzymes prior to treatment.

If new or worsening liver dysfunction (including significant elevation of liver enzymes and/or symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, hepatomegaly) develops in patients using PREZISTA/rtv, interruption or discontinuation of treatment must be considered. When deciding to re-initiate a drug that may have induced hepatotoxicity, physicians should be aware that more severe hepatic injury may ensue.

Tibotec is working with Health Canada to incorporate this new safety information in the Canadian Product Monograph for PREZISTA.

Managing marketed health product-related adverse reactions depends on health care professionals and consumers reporting them. Reporting rates determined on the basis of spontaneously reported post-marketing adverse reactions are generally presumed to underestimate the risks associated with health product treatments. Any case of serious hepatotoxicity or other serious or unexpected adverse reactions in patients receiving PREZISTA should be reported to Tibotec or Health Canada at the following addresses:

Tibotec, a division of Janssen-Ortho Inc.
Drug Safety Department
19 Green Belt Drive
Toronto, ON M3C 1L9
Tel: (800) 567-3331 or Fax: (866) 767-5865

Any suspected adverse reaction can also be reported to:
Canada Vigilance Program
Marketed Health Products Directorate
HEALTH CANADA
Address Locator: 0701C
Ottawa, Ontario, K1A 0K9
Tel: 613-957-0337 or Fax: 613-957-0335
To report an Adverse Reaction, consumers and health professionals may call toll free:
Tel: 866-234-2345
Fax: 866-678-6789
CanadaVigilance@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.*

http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/ar-ei_form_e.html
http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/guide/ar-ei_guide-ldir_e.html

For other inquiries related to this communication, please contact Health Canada at:
Bureau of Gastroenterology, Infection and Viral Diseases (BGIVD)
E-mail: BGIVD_Enquiries@hc-sc.gc.ca
Tel: 613-941-2566
Fax: 613-941-1183

Sincerely,

Cathy Lau, PhD.

Vice President
Regulatory Affairs
Janssen-Ortho Inc.