JANSSEN-ORTHO Inc.

ORTHO BIOTECH

IMPORTANT NEW SAFETY INFORMATION

EPREX* (epoetin alfa): reports of pure red blood cell aplasia

November 26, 2001

Dear Healthcare Professional:

Please carefully review the safety information below, in particular the information in the boxed section.

Janssen-Ortho Inc., following discussions with Health Canada, would like to inform you of important new safety information for EPREX (epoetin alfa), a biological therapeutic product that has been approved in Canada for the treatment of anemia associated with chronic renal failure (CRF), cancer or concomitantly administered cancer chemotherapy, zidovudine-treated/HIV-infected patients and for use in patients undergoing autologous blood donation, and to reduce allogenic blood exposure for patients undergoing elective surgery. Cases of pure red blood cell aplasia (PRCA) have been reported from post-marketing experience in patients with CRF, most of them being treated with EPREX or other erythropoietins.

In Canada, there has been an estimated 80,000 patient years of exposure to EPREX in patients with renal failure. In 15 countries surveyed (including those where cases have been reported), an estimated 800,000 renal failure patients have been treated with EPREX. As of 15 September 2001, 40 cases of confirmed or suspected PRCA have been reported from various countries in the world in CRF patients treated with EPREX, most occurring after 1998. In Canada, there have been 7 reports of confirmed or suspected PRCA in patients treated with EPREX. The overall estimated reporting rate of the event in the 15 countries appears to be less than 1:10,000 in CRF patients. Typically, following months to years after initiation of therapy, patients developed sudden worsening of anemia unresponsive to increasing doses of erythropoietin. PRCA was confirmed by bone marrow evaluation and in most cases neutralizing antibodies to erythropoietin were detected in serum. All of these patients became transfusion-dependent and did not respond to other erythropoietins when treatment was tried following the diagnosis or suspicion of PRCA.

Physicians are advised to monitor clinical response to EPREX. In patients developing sudden lack of efficacy, or worsening of anemia, typical causes of non-response (e.g. iron folate and Vitamin B_{12} deficiency, aluminum intoxication, infection or inflammation, blood loss, and haemolysis) should be investigated. **If PRCA is suspected and no cause can be identified, testing for erythropoietin antibodies and bone marrow examinations should be considered and therapy with EPREX must be discontinued immediately. Patients should NOT be switched to another erythropoietin.** Other causes of pure red cell aplasia should be excluded, and appropriate therapy instituted.

Janssen-Ortho Inc. has proposed revisions to the Prescribing Information to reflect this updated safety information in the **Warnings** and **Adverse Reactions** sections which are currently under review by Health Canada. The revised Prescribing Information will be available on the Janssen-Ortho Inc. web site and in the next edition of *The Compendium of Pharmaceuticals and Specialties* following approval by Health Canada. Clinicians and pharmacists are advised to properly handle the product as emphasized in the Prescribing Information, by storing the product at 2˚ to 8˚C in its

original outer package and not freezing. Clinicians are also advised to review the handling and storage information with their patients, as described in the Patient Package Insert.

Reporting rates determined on the basis of spontaneously reported post-marketing adverse events are generally presumed to underestimate the risks associated with drug treatments.

The identification, characterization, and management of drug-related adverse events are dependent on the active participation of healthcare professionals in adverse drug reaction reporting programmes. Any occurrences of PRCA or other serious and/or unexpected adverse events in patients receiving EPREX should be reported to Janssen-Ortho Inc. or the Bureau of Licensed Product Assessment at the following addresses:

Janssen-Ortho Inc.
19 Green Belt Drive
Toronto, ON
M3C 1L9

Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Bureau of Licensed Product Assessment
Therapeutic Products Programme
HEALTH CANADA
Address Locator: 0201C2
OTTAWA, Ontario, K1A 1B9
Tel: (613) 957-0337 or Fax: (613) 957-0335
Toll Free Tel: (866) 234-2345
Toll Free Fax: (866) 678-6789
cadrmp@hc-sc.gc.ca

The ADR Reporting Form can be found in *The Compendium of Pharmaceuticals and Specialties* and on the TPD web site along with the ADR Guidelines at:

http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/forms/adverse_e.pdf
http://www.hc-sc.gc.ca/hpb-dgps/therapeut/zfiles/english/guides/adr/adr_guideline_e.pdf

Your professional commitment in this regard has an important role in protecting the well-being of your patients by contributing to early signal detection and informed drug use.

Should you have any questions or require additional information concerning the use of EPREX, please contact Janssen-Ortho Inc. Medical Information Department at 1-800-567-3331 from 9:00 a.m. to 5:00 p.m. Monday to Friday, Eastern Standard Time or access our web site at http://www.janssen-ortho.com.

Sincerely,

Wendy Arnott, Pharm.D
Vice-President
Medical, Regulatory, Quality, Linguistics
Janssen-Ortho Inc.

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