JANSSEN-ORTHO

ORTHO BIOTECH
DIVISION OF JANSSEN-ORTHO INC.

Important Drug Safety Update

EPREX* (epoetin alfa) – Pure Red Cell Aplasia (PRCA, Erythroblastopenia)

June 25, 2002

Dear Healthcare Professional:

Please review the information below, in particular the bolded information in the boxed section.

Janssen-Ortho Inc. (The Company) following discussions with Health Canada, informed you in a letter dated November 26, 2001, of post-marketing reports of pure red cell aplasia (PRCA, erythroblastopenia) in patients with chronic renal failure (CRF) after months to years of treatment with EPREX (epoetin alfa) or other erythropoietin products. The purpose of this letter is to provide the extent of, and most recent information regarding the worldwide reported cases of PRCA in patients treated with EPREX as of April 30, 2002.

The Company has embarked on a comprehensive technical and clinical investigation into possible triggers of PRCA. Based on the investigation to date, no single trigger has been identified and a number of factors may contribute to the development of immunogenicity of the exogenous protein, epoetin, and all possible factors are being explored.

The scientific literature to date suggests that all exogenous proteins have the potential to elicit an immune response, particularly when administered via the subcutaneous route[1]. Consequently, while The Company continues further investigation of the multiple aspects contributing to antibody formation and PRCA in patients, the product should be administered by the IV route in CRF patients (predialysis, hemodialysis and peritoneal dialysis), where feasible. If IV access is not feasible in a patient with CRF, the risk/benefit of SC administration should be considered for each patient.

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 no cause can be identified for the anemia and PRCA is suspected, 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 PRCA should be excluded, and appropriate therapy instituted. If PRCA is suspected in a patient being administered EPREX, please contact The Company for antibody testing.

The Company is aware of 124 worldwide post-marketing reports of suspected PRCA in CRF patients treated with EPREX of which 104 are reported to have been confirmed by bone marrow examination. Antibodies to erythropoietin have been observed in 63 (out of 79 for whom results were available) EPREX treated patients diagnosed with PRCA. All of these cases were reported in CRF patients (pre-dialysis, peritoneal dialysis and hemodialysis) and are displayed in the table below. The median onset of PRCA was 11 months with a range of 1-92 months from the initiation of EPREX therapy. To date, one death has been related to the treatment of PRCA with immunosuppressive therapy.

Suspected PRCA Cases Reported and EPREX Exposure Worldwide by Year as of April 30, 2002

	Year Unknown	Prior to 1999	1999	2000	2001	2002 YTD
# of Suspected PRCA Cases by Year of Onset	28	3	11	16	57	9
Exposure to EPREX (100,000 patient-years)		8.93	2.09	2.26	2.48	0.88

[1] Porter S. Human immune response to recombinant human proteins. J. Pharm. Sci 2001; 90:1.

19 Green Belt Drive, Toronto, Ontario, Canada M3C 1L9

In Canada, as of April 30 2002, there have been 27 post-marketing reports of suspected PRCA. Of these, 20 cases (with sufficient data following medical review) have been included in these analyses by The Company. Estimated EPREX exposure rate in CRF patients in Canada is 1.02×10^5 patient-years, giving a reported Canadian incidence rate for suspected PRCA of 19.6 per 100,000 patient-years. Estimated worldwide EPREX exposure is 16.62×10^5 patient-years, giving a worldwide reporting incidence rate for suspected PRCA of 7.5 per 100,000 patient-years.

Most of the worldwide reports of PRCA are associated with the subcutaneous route (SC) of administration. Since the mid 1990's, administration of EPREX in CRF patients has changed from a predominantly intravenously administered product to a predominantly subcutaneous administered product in most countries. Based on available exposure data from a limited number of countries (Canada, Finland, France, Germany, Italy, Norway, Spain, Switzerland, Sweden and United Kingdom), the estimated reporting incidences of suspected PRCA cases for the period 1998 to 2002 have been calculated as 0.66 / 100,000 patient-years for the intraveneous route and 19.57 / 100,000 patient-years for the SC route.

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 Marketed Health Products Directorate, Health Products and Food Branch, Health Canada at the following addresses:

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

Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Marketed Health Products Directorate
Health Products and Food Branch
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

Information on adverse reaction reporting may be obtained at the following website address:
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 website at http://www.janssen-ortho.com.

Sincerely,

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

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