JANSSEN-ORTHO

IMPORTANT DRUG SAFETY INFORMATION

EPREX* (epoetin alfa) Sterile Solution
REVISED PRESCRIBING INFORMATION REGARDING THROMBOTIC VASCULAR EVENTS RELATED TO HIGH HEMOGLOBIN LEVELS IN PATIENTS WITH CANCER

October 13, 2004

Dear Healthcare Professional:

Janssen-Ortho Inc., in consultation with Health Canada, has revised the following sections of the Product Monograph for EPREX (epoetin alfa): Contraindications, Warnings, Precautions, Adverse Reactions, Dosage and Administration, and Information for the Patient. This action has been taken in keeping with our commitment to healthcare professional education, and the safe and proper use of our products.

The following information is relevant to patients with cancer:

- **Recent Investigational Clinical Trials with erythropoiesis regulating hormones, including EPREX, have evaluated treatment of cancer patients to target hemoglobin levels beyond the correction of anemia (i.e. greater than 120 grams per litre). An increased frequency of adverse patient outcomes, including increased mortality and thrombotic vascular events, was reported in some of these studies.**
- **Three small investigational, randomized, controlled oncology studies (n = 60-113), where patients with cancer who were receiving chemotherapy with or without radiation therapy were treated with epoetin alfa to hemoglobin levels higher than 120 g/L, were suspended due to increased incidence of TVEs in epoetin alfa-treated patients (16-34%) compared with placebo-treated patients (5-6%).** [1]
- **The target hemoglobin concentration should be 120 g/L.**
- **If hemoglobin increases by more than 10 g/L in a 2-week period or if the hemoglobin exceeds 120 g/L, the dose should be reduced by approximately 25%. If the hemoglobin exceeds 130 g/L, doses should be temporarily withheld until the hemoglobin falls to 120 g/L and then reinitiated at the dose approximately 25% below the previous dose.**

Thrombotic Vascular Events (TVEs) have been reported with the use of erythropoietic agents. Patients with cancer are generally at higher risk of TVEs than other patient populations as a result of known risk factors such as malignancy, chemotherapy and radiation therapy.[2]

Please refer to the attached highlighted copy of the Prescribing Information for other important related revisions to the other sections. Please insert this revised Prescribing Information in your copy of the Compendium of Pharmaceuticals and Specialties (CPS) and use when prescribing or dispensing EPREX (epoetin alfa). The revised Product Monograph is also available on the Janssen-Ortho website at http://www.janssen-ortho.com. EPREX is a safe and effective treatment for anemia when used in accordance with the approved Prescribing Information.

Janssen-Ortho Inc. will continue to monitor ongoing clinical trials, and worldwide pharmacovigilance reports.

The identification, characterization, and management of marketed health product-related adverse reactions are dependent on the active participation of healthcare professionals in adverse drug reaction reporting programmes. Any occurrences of serious and/or unexpected adverse reactions in patients receiving EPREX (epoetin alfa) should be reported to Janssen-Ortho Inc. or the Marketed Health Products Directorate at the following addresses:

Janssen-Ortho Inc.
19 Green Belt Drive
Toronto, Ontario
M3C 1L9
Or call toll-free at 1-800-567-3331
Or email to dsscan@joica.jnj.com
Or fax to 416-449-2658

Any suspected adverse incident 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
Local Tel: (613) 957-0337 or Local Fax: (613) 957-0335
Toll-Free Tel: (866) 234-2345 or Toll-Free Fax: (866) 678-6789
cadrmp@hc-sc.gc.ca

The ADR Reporting Form can be found in *The Canadian Compendium of Pharmaceuticals and Specialties*, or on the TPD website, along with the ADR Guidelines at:
www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/adverse_e.pdf
www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/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 regarding the use of EPREX (epoetin alfa), please contact Janssen-Ortho Inc. Medical Information Department at 1-800-567-3331 from 9:00 am to 5:00 pm Monday to Friday Eastern Standard Time (EST) or by Facsimile at 416-449-2658. A copy of this letter is also available on the Janssen-Ortho website at http://www.janssen-ortho.com and on the Health Canada website at http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_e.html.

Sincerely,

Wendy Arnott, Pharm.D.
Vice President
Regulatory, Safety and Quality

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[1] FDA Briefing Document for Oncologic Drugs Advisory Committee Meeting (May 4, 2004). Safety Concerns Associated With Aranesp (Darbepoetin Alfa) Amgen, Inc. and Procrit (Epoetin Alfa) Ortho Biotech, L.P., for the Treatment of Anemia Associated With Cancer Chemotherapy, pages 50, 53, 56. http://www.fda.gov/ohrms/dockets/ac/04/briefing/4037b2_04.pdf

[2] Lee AYY, Levine MN. Venous thromboembolism and cancer: Risks and outcomes. *Circulation* 2003; 107: I-17 - I-21.