

**Health Canada Endorsed Important Safety Information on
Erythropoiesis-Stimulating Agents (ESAs):
Aranesp® (darbepoetin alfa) and EPREX* (epoetin alfa)**



JANSSEN-ORTHO

April 16, 2007

Dear Healthcare Professional:

Subject: Important Safety Information and New Prescribing Information for the Erythropoiesis-Stimulating Agents, Aranesp® (darbepoetin alfa) and EPREX* (epoetin alfa)

The manufacturers of the erythropoiesis-stimulating agents (ESAs), in consultation with Health Canada, would like to inform you of updated safety information and pending label changes based on completed or ongoing clinical studies regarding treatment with ESAs. Two such ESAs, Aranesp® and EPREX, are marketed in Canada.

Aranesp® is indicated for the treatment of anemia associated with chronic renal failure, and for the treatment of anemia in patients with non-myeloid malignancies, where anemia is due to the effect of concomitantly administered chemotherapy.

EPREX is indicated for the treatment of anemia associated with chronic renal failure, the treatment of anemia in patients with non-myeloid malignancies, where anemia is due to the effect of concomitantly administered chemotherapy, the treatment of anemia in zidovudine-treated/HIV-infected patients, and for the treatment of patients undergoing major elective surgery to facilitate autologous blood collection, and to reduce allogeneic blood exposure.

As a result of these updates, EPREX is no longer indicated in the treatment of anemia in patients with non-myeloid malignancies, where anemia is due to the disease itself. Therefore, none of the ESAs are indicated in this patient population.

Recent clinical study results summarized below have suggested higher risks of certain adverse events when patients were treated to target hemoglobin levels of greater than 120 g/L. The manufacturers are working with Health Canada to update their respective Canadian Product Monographs to reflect the current status of knowledge on the safety of these products.

- **Healthcare professionals are advised to titrate the dose of ESA that will gradually increase the hemoglobin concentration to the lowest level sufficient to avoid blood transfusions. Hemoglobin levels during ESA treatment should not exceed 120 g/L. (May not be applicable to all surgery patients, see below).**
- **Patients treated with EPREX prior to elective surgery, for the purposes of reducing the requirements for allogeneic blood transfusion, should receive adequate antithrombotic prophylaxis in order to reduce the incidence of deep venous thrombosis.**
- **ESAs increased the risk of death and of serious cardiovascular adverse events in patients with cancer or renal failure, when treated to a target hemoglobin level of greater than 120 g/L.**
- **An increased risk of death was seen in cancer patients with active malignant disease, who were not being treated with either radiation or chemotherapy and who were treated with ESAs to a target hemoglobin level of 120 g/L. ESAs are not indicated in this patient population.**
- **ESAs shortened the time to tumour progression in patients with advanced head and neck cancer receiving radiation therapy; in addition, ESAs decreased overall survival and increased deaths at 4 months, attributed to disease progression in patients with metastatic breast cancer receiving chemotherapy, when these groups of patients were treated to a target hemoglobin level of greater than 120 g/L.**

Recent clinical studies have provided new safety information regarding the use of ESAs, including risks of tumour progression and serious cardiovascular events:

1. A randomized prospective trial¹ evaluated 1432 anemic chronic renal failure patients who were not undergoing dialysis. Patients were assigned to epoetin alfa treatment targeting a maintenance hemoglobin concentration of 135 g/L or 113 g/L. A major cardiovascular event (death, myocardial infarction, stroke or hospitalization for congestive heart failure) occurred among 125 (18%) of the 715 patients in the higher hemoglobin group compared to 97 (14%) among the 717 patients in the lower hemoglobin group (hazard ratio [HR] 1.3, 95% CI: 1.0, 1.7, p = 0.03).
2. Another randomized controlled clinical study evaluated 939 mainly non-anemic women with metastatic breast cancer receiving chemotherapy². Patients received either weekly epoetin alfa or placebo for up to a year. This study was designed to show that survival was superior when epoetin alfa was administered to prevent anemia (maintain hemoglobin levels between 120 and 140 g/L). The study was terminated prematurely when interim results demonstrated that higher mortality at 4 months (8.7% epoetin alfa vs 3.4% placebo) and a higher rate of fatal thrombotic events (1.1% epoetin alfa vs 0.2% placebo) were observed among patients treated with epoetin alfa. Based on Kaplan-Meier estimates, at the time of study termination, the 12-month survival was lower in the epoetin alfa group than in the placebo group (70% vs 76%, HR 1.37, 95% CI: 1.07, 1.75, p = 0.012).
3. A recently-completed phase III double-blind, randomized, placebo-controlled trial evaluating 989 cancer patients with active malignant disease, but not being treated with either chemotherapy or radiation therapy showed no statistically-significant reduction in the proportion of patients receiving red blood cell transfusions, and more deaths in the darbepoetin alfa group than in the placebo group (26% vs 20%) at 16 weeks³ (completion of treatment phase). With a median

survival follow-up of 4.3 months, the absolute number of deaths at the end of the study was also higher in the darbepoetin alfa group (49% vs 46%, HR 1.29, 95% CI: 1.08, 1.55).

4. A preliminary report from a clinical study evaluating 522 patients with primary squamous cell carcinoma of the head and neck receiving radiation therapy demonstrated a 10% increase in locoregional failure rate among darbepoetin alfa-treated patients ($p=0.01$) in an interim analysis in 484 patients. Patients were randomized to darbepoetin alfa or placebo. At the time of study termination, there was a trend toward worse survival in the darbepoetin group ($p = 0.08$)⁴.
5. In a multicentre, randomized, double-blind placebo-controlled trial, patients with advanced non-small-cell lung cancer unsuitable for curative therapy were treated with epoetin alfa targeting hemoglobin levels between 120 and 140 g/L or placebo. Following an interim analysis of 70 of 300 patients planned, a significant difference in median survival in favour of patients in the placebo group was observed (63 vs 129 days, HR 1.84, $p = 0.04$)⁵.
6. A randomized controlled study in which 681 adult patients not receiving prophylactic anticoagulation and undergoing spinal surgery received either 4 doses of 600 U/kg epoetin alfa (7, 14 and 21 days before surgery and on the date of surgery) and standard of care treatment, or standard of care treatment alone. Preliminary analysis showed a higher incidence of deep vein thrombosis, determined by either Colour Flow Duplex Imaging or by clinical symptoms in the epoetin alfa group [16 patients (4.7%)] compared to the standard of care group [7 patients (2.1%)]. In addition, 12 patients in the epoetin group and 7 patients in the standard of care group had other thrombotic vascular events⁶.

Although the current Canadian Product Monograph for EPREX provides adequate guidance for use in patients undergoing major elective surgery, based on this information, healthcare professionals are reminded that surgical patients receiving EPREX prior to elective surgery, in order to reduce the requirements for allogeneic blood transfusion should receive adequate antithrombotic prophylaxis in order to reduce the incidence of documented deep venous thrombosis.

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 cardiovascular events, tumour progression or other serious or unexpected adverse reactions in patients receiving ESAs should be reported to Amgen Canada (Aranesp[®]), Janssen-Ortho, Inc. (EPREX) or Health Canada at the following addresses:

Aranesp®

Amgen Canada, Inc.
6755 Mississauga Road, Suite 400
Mississauga, Ontario L5N 7Y2
Tel: (866) 502-6436 or Fax: (888) 264-3655
safetycanada@amgen.com

EPREX

Janssen-Ortho Inc.
19 Green Belt Drive
Toronto, ON M3C 1L9
Tel: (800) 567-3331 or Fax: (866) 767-5865
dsscscan@joica.jnj.com

Any suspected adverse reaction 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
To report an Adverse Reaction, consumers and health professionals may call toll free:
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*.

http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/form/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:

Marketed Health Products Directorate (MHPD)
E-mail: mhpd_dpsc@hc-sc.gc.ca
Tel: (613) 954-6522
Fax: (613) 952-7738

Sincerely,



David N. Churchill, MD, FRCPC
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Cathy Lau, PhD.
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References:

1. Singh AK, Szczech L, Tang KL, *et al.* Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med.* 2006 355(20):2085-98.
2. Leyland-Jones B, Semiglazov V, Pawlicki M, *et al.* Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. *J Clin Oncol.* 2005 23(25):5960-72.
3. http://clinicalstudyresults.org/documents/company-study_2157_0.pdf
4. http://frejacms.au.dk/dahanca/get_media_file.php?mediaid=125
5. Wright JR, Ung YC, Julian JA, *et al.* Randomized, Double-Blind, Placebo-Controlled Trial of Erythropoietin in Non-Small-Cell Lung Cancer With Disease-Related Anemia. *J Clin Oncol.* 2007 25(9):1-6
6. http://download.veritasmedicine.com/PDF/CR004621_ToplineResults.pdf

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