IRISH MEDICINES BOARD

14/07/08

To Healthcare Professionals

**SUBJECT: Conclusions from the EU Review of the Safety of Erythropoiesis Stimulating Agents (ESAs) in Patients with anaemia resulting from renal insufficiency or chemotherapy in cancer patients**

**Epoetin alfa (EPREX®)**
**Darbepoetin alfa (ARANESP® /NESPO®)**
**Epoetin beta (NEORECORMON®)**
**Methoxy polyethylene glycol-epoetin beta (MIRCERA®)**
**Epoetin delta (DYNEPO®)**
**Biosimilar Epoetin alfa (BINOCRIT/EPOETIN ALFA HEXAL/ABSEAMED)**
**Biosimilar Epoetin Zeta (SILAPO/RETACRIT)**

Dear Healthcare Professional,

The European Medicines Agency (EMEA) and the Irish Medicines Board (IMB) wish to provide you with important new information regarding the safety of Erythropoiesis Stimulating Agents (ESAs).

Over the last years, results from randomised controlled clinical studies, meta-analyses and a Cochrane Review have raised concerns about:

- Shortened time to tumour progression, reduced overall survival and increased risk of venous thromboembolism in cancer patients treated with ESAs.
- Increased risk of death and serious cardiovascular events in anaemic patients with chronic renal failure treated with ESAs, when haemoglobin exceeds a concentration of 12 g/dL.

Following review of all available data, the EMEA's Committee for Medicinal Products for Human Use (CHMP) and its Pharmacovigilance Working Party (PhVWP) concluded that the benefits of these products continue to outweigh their risks in the approved indications. However, the CHMP recommended changes to the product information, and in February 2008 the European Commission made the final decision to amend the product information for all ESAs.

Where appropriate, procedures are underway to update the SmPCs regarding the recommended conditions for use of ESAs, as follows:

- Criteria for administration of ESAs to patients with symptomatic anaemia associated with renal insufficiency or non-myeloid malignancies.
- The lowest dose of ESA should be administered to maintain haemoglobin concentration within the range 10 – 12 g/dL, and
- To advise that blood transfusions may be the preferred treatment option in certain therapeutic situations in cancer patients with chemotherapy-related anaemia. The decision to administer ESAs should be based on an informed risk-benefit assessment with the participation of the individual patient and should take into account the type of tumour and its stage; the degree of anaemia; cancer prognosis; the treatment environment; and patient preference.

These important changes have been addressed, for the renal and oncology indications, in the following sections: 4.1 (Indications), 4.2 (Posology), 4.4 (Special Warnings and Precautions, a section that has been further updated in June 2008 following recent new study data)**,** and 5.1 (Pharmacodynamic properties).

The revised version of the relevant sections in the SmPC is attached to this letter (annex 1 renal indications and annex 2 oncology).

Marketing authorisation holders are conducting further studies to investigate the risks highlighted in this communication and further information should become available in due course. Prescribers are urged to prescribe ESAs according to their approved indications only.

Suspected adverse reactions related to use of an ESA should be reported to the IMB and/or the relevant company in accordance with normal procedures.

Should you have any questions or require further information regarding the use of ESAs, please contact the relevant company or the IMB.

Yours sincerely,

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**Dr. Joan Gilvarry, MB., FRCPI.,**
**Director of Human Medicines**

*Epoetin delta (DYNEPO®) and Methoxy-polyethyleneglycol-epoetin beta (MIRCERA®) are approved for the treatment of symptomatic anaemia in patients with chronic renal failure. It may be used in patients on dialysis and patients not on dialysis. DYNEPO® and MIRCERA® are not approved for the treatment of symptomatic anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy.

**Revised sections of SmPCs:**
**Compilation of amended wording for SmPCs for all epoetins**

## Annex 1: Renal indication

**Section 4.1**

"Treatment of symptomatic anaemia associated with chronic renal failure (CRF) in adult and paediatric patients."

**Section 4.2**

"Treatment of symptomatic anaemia in adult and paediatric chronic renal failure patients

Anaemia symptoms and sequelae may vary with age, gender, and overall burden of disease; a physician's evaluation of the individual patient's clinical course and condition is necessary. ESA should be administered either subcutaneously or intravenously in order to increase haemoglobin to not greater than 12 g/dL (7.5 mmol/L). Subcutaneous use is preferable in patients who are not receiving haemodialysis to avoid puncture of peripheral veins.
Due to intra-patient variability, occasional individual haemoglobin values for a patient above and below the desired haemoglobin level may be observed. Haemoglobin variability should be addressed through dose management, with consideration for the haemoglobin target range of 10g/dL (6.2 mmol/l) to 12g/dL (7.5mmol/l). A sustained haemoglobin level of greater than 12g/dL (7.5mmol/l) should be avoided; guidance for appropriate dose adjustment for when haemoglobin values exceeding 12g/dL (7.5mmol/l) are observed are described below.

A rise in haemoglobin of greater than 2g/dL (1.25 mmol/l) over a four week period should be avoided. If it occurs, appropriate dose adjustment should be made as provided.

Patients should be monitored closely to ensure that the lowest approved dose of ESA is used to provide adequate control of the symptoms of anaemia.

**Section 4.4**

"In patients with chronic renal failure, maintenance haemoglobin concentration should not exceed the upper limit of the target haemoglobin concentration recommended in section 4.2. In clinical trials, an increased risk of death and serious cardiovascular events was observed when erythropoiesis stimulating agents (ESAs) were administered to target a haemoglobin of greater than 12g/dL (7.5 mmol/l).
Controlled clinical trials have not shown significant benefits attributable to the administration of epoetins when haemoglobin concentration is increased beyond the level necessary to control symptoms of anaemia and to avoid blood transfusion.

## Annex 2: Chemotherapy induced anaemia in patients with cancer

**Section 4.2**

"Treatment of patients with chemotherapy induced anaemia
ESA should be administered by the subcutaneous route to patients with anaemia (e.g. haemoglobin concentration ≤ 10g/dL (6.8 mmol/L). Anaemia symptoms and sequelae may vary with age, gender, and overall burden of disease; a physician's evaluation of the individual patient's clinical course and condition is necessary.
Due to intra-patient variability, occasional individual haemoglobin values for a patient above and below the desired haemoglobin level may be observed. Haemoglobin variability should be addressed through dose management, with consideration for the haemoglobin target range of

10g/dL (6.2 mmol/l) to 12g/dL (7.5mmol/l). A sustained haemoglobin level of greater than 12g/dL (7.5mmol/l) should be avoided; guidance for appropriate dose adjustment for when haemoglobin values exceeding 12g/dL (7.5mmol/l) are observed are described below.
"Patients should be monitored closely to ensure that the lowest approved dose of ESA is used to provide adequate control of the symptoms of anaemia."

Dosage adjustment to maintain haemoglobin concentrations between 10g/dL – 12g/dL:

"Treatment of symptomatic chemotherapy induced anaemia in cancer patients
Once the therapeutic objective for an individual patient has been achieved, the dose should be reduced by 25 to 50% in order to maintain haemoglobin at that level. Appropriate dose titration between (to be detailed for the specific ESA) should be considered.
If the haemoglobin exceeds 12 g/dL (7.5 mmol/l), the dose should be reduced by approximately 25 to 50%. Treatment with ESA should be temporarily discontinued if haemoglobin levels exceed 13 g/dL (8.1 mmol/L). Therapy should be reinitiated at approximately 25% lower than the previous dose after haemoglobin levels fall to 12 g/dL (7.5 mmol/L) or below."

**Section 4.4**

"Epoetins are growth factors that primarily stimulate red blood cell production. Erythropoietin receptors may be expressed on the surface of a variety of tumour cells. As with all growth factors, there is a concern that epoetins could stimulate the growth of tumours. In several controlled studies, epoetins have not been shown to improve overall survival or decrease the risk of tumour progression in patients with anaemia associated with cancer.

In controlled clinical studies, use of ESA and other erythropoiesis-stimulating agents (ESAs) have shown:

- shortened time to tumour progression in patients with advanced head and neck cancer patients receiving radiation therapy when administered to target a haemoglobin of greater than 14 g/dL (8.7 mmol/L),
- shortened overall survival and increased deaths attributed to disease progression at 4 months in patients with metastatic breast cancer receiving chemotherapy when administered to target a haemoglobin of 12-14 g/dL (7.5-8.7 mmol/L),
- increased risk of death when administered to target a haemoglobin of 12 g/dL (7.5 mmol/L) in patients with active malignant disease receiving neither chemotherapy nor radiation therapy. ESAs are not indicated for use in this patient population."

In view of the above, in some clinical situations blood transfusion should be the preferred treatment for the management of anaemia in patients with cancer. The decision to administer recombinant erythropoietin treatment should be based on a benefit-risk assessment with the participation of the individual patient, which should take into account the specific clinical context. Factors that should be considered in this assessment should include the type of tumour and its stage; the degree of anaemia; life-expectancy; the environment in which the patient is being treated; and patient preference (see section 5.1)."

**Section 5.1**

Erythropoietin is a growth factor that primarily stimulates red cell production. Erythropoietin receptors may be expressed on the surface of a variety of tumour cells.

Survival and tumour progression have been examined in five large controlled studies involving a total of 2833 patients, of which four were double-blind placebo-controlled studies and one was an open-label study. Two of the studies recruited patients who were being treated with chemotherapy. The target haemoglobin concentration in two studies was >13 g/dL; in the remaining three studies it was 12-14 g/dL. In the open-label study there was no difference in overall survival between patients treated with recombinant human erythropoietin and controls. In the four placebo-controlled studies the hazard ratios for overall survival ranged between 1.25 and 2.47 in favour of controls. These studies have shown a consistent unexplained statistically significant excess mortality in patients who have anaemia associated with various common cancers who received recombinant human erythropoietin compared to controls. Overall survival outcome in the trials could not be satisfactorily explained by differences in the incidence of thrombosis and related complications between those given recombinant human erythropoietin and those in the control group.

A systematic review has also been performed involving more than 9000 cancer patients participating in 57 clinical trials. Meta-analysis of overall survival data produced a hazard ratio point estimate of 1.08 in favour of controls (95% CI: 0.99, 1.18; 42 trials and 8167 patients). An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06, 35 trials and 6769 patients) was observed in patients treated with recombinant human erythropoietin. There is therefore consistent evidence to suggest that there may be significant harm to patients with cancer who are treated with recombinant human erythropoietin. The extent to which these outcomes might apply to the administration of recombinant human erythropoietin to patients with cancer, treated with chemotherapy to achieve haemoglobin concentrations less than 13 g/dL, is unclear because few patients with these characteristics were included in the data reviewed.

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