



London, 23 October 2007  
Doc. Ref. EMEA/496188/2007

## Public Statement

### **Epoetins and the risk of tumour growth progression and thromboembolic events in cancer patients and cardiovascular risks in patients with chronic kidney disease**

The European Medicines Agency (EMA) has recently reviewed the safety of epoetins. These medicines are used for the treatment of anaemia in patients with chronic renal failure and for the treatment of patients with non-myeloid malignancies receiving chemotherapy.

The safety review was initiated because data from recent clinical trials show a consistent unexplained excess mortality in patients with anaemia associated with cancer who have been treated with epoetins. In addition, the results of two studies and a meta-analysis have recently been published suggest that treatment of anaemia with epoetins in patients with chronic kidney disease to achieve relatively high target haemoglobin concentrations may be associated with an increase in the risk of mortality and cardiovascular morbidity.

#### **Conclusions**

Following review of all available data, the EMA'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, but recommended the following changes to the product information:

#### PRODUCT USAGE

- Changes to the 'Indication' section (section 4.1), saying that epoetins should be used in the treatment of anaemia only if associated with symptoms.
- Changes to the 'Posology' section (Section 4.2), stipulating a uniform target haemoglobin range for all epoetins of 10 g/dL to 12 g/dL with a warning not to exceed a concentration of 12 g/dL.

#### ADDITIONAL INFORMATION

- Changes to the 'Special Warnings and Precautions for Use' section (Section 4.4), adding an explanation that trials have shown a small unexplained excess mortality in association with high target haemoglobin concentrations and they have not shown significant benefits attributable to the administration of epoetins to increase haemoglobin concentration beyond the level necessary to control symptoms of anaemia and to avoid blood transfusion.
- Changes to the 'Pharmacodynamic properties' section (section 5.1) to include new information on results of clinical trials which have shown significant excess mortality in patients who have anaemia associated with various common cancers who received epoetins compared with those who did not receive epoetins.

Healthcare professional should use epoetins strictly in accordance with their approved Summaries of Product Characteristics, regarding the indications and dosing recommendations.

## Implementation

The changes will now be implemented throughout the European Union. The EMEA has requested all Marketing Authorisation Holders for centrally authorised epoetins (Aranesp/Nespo, Dynepo, Mircera, NeoRecormon, Binokrit, Epoetin Alfa Hexal, Abseamed) to submit an application for a type II-variation to the marketing authorisation. For medicinal products that are authorised at the level of the Member States (Eprex), the national competent authorities in the Member States will take further action as appropriate.

The CHMP also concluded that there is a need to increase the scientific knowledge on the effects of epoetins. Marketing Authorisation Holders have been asked to combine all available patient-level data jointly in order to provide further confirmation of the provisionally accepted conclusion that anaemic patients receiving chemotherapy showed no evidence of an adverse impact on survival and to perform additional studies to assess the functional activity of epoetin receptors in different tumour types, and at different stages in the life-cycle of tumour evolution.

The CHMP will continue to review the safety profile of the epoetins within the terms of their currently authorised indications in the EU as additional data becomes available.

## References

1. Ajay K Singh *et al.* for the CHOIR Investigators. *Correction of Anaemia with Epoetin Alfa in Chronic Kidney Disease.* *N Engl J Med* 2006; 355:2058-98
2. Tilman B Drüeke *et al.* for the CREATE Investigators. *Normalization of Haemoglobin Level in Patients with Chronic Kidney Disease and Anaemia.* *N Engl J Med* 2006; 355: 2071-84
3. Phrommintikul A *et al.*: *Mortality and Target Haemoglobin Concentrations in Anaemic Patients with Chronic Kidney Disease Treated with erythropoietin: a Meta-Analysis.* *Lancet* 2007; 369: 381-88

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