European Medicines Agency

Product name: **NEORECORMON**
Procedure No. **EMEA/H/C/116/II/37**

SUMMARY OF THE SCIENTIFIC DISCUSSION

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Following the publication of two clinical studies showing an increased mortality in cancer patients who were administered epoetin alfa (*Leyland-Jones B, 2003*) or epoetin beta (*Henke M et al, 2003*) respectively, the Pharmacovigilance Working Party (PhVWP) looked at the risk of tumour growth progression and thromboembolism in patients with cancer treated with epoetins. Further to the recommendations of the PhVWP the CHMP requested further advice from the Scientific Advisory Group for Oncology. As a result, relevant parts of sections 4.1, 4.2, 4.4 and 5.1 of the SPC for the different epoetins centrally authorised in the treatment of anaemic cancer patients receiving chemotherapy were amended as detailed below.

The baseline, target and maximum corrected Hb values and the dose monitoring were revised in section 4.2 as follows:

"NeoRecormon treatment is indicated if the haemoglobin value is ~~≤ 13 g/dl (8.07 mmol/l)~~ ≤ 11 g/dl (6.83 mmol/l) ~~at the start of chemotherapy~~. The recommended initial dose is 450 IU/kg body weight per week…

Haemoglobin level should not exceed 13 g/dl (8.07 mmol/l) (see section 5.1)….

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. If required, further dose reduction may be instituted to ensure that haemoglobin level does not exceed 13 g/dl.

If the rise in haemoglobin is greater than 2 g/dl (1.3 mmol/l) in 4 weeks, the dose should be reduced by 25 to 50%."

The following warning on the effect of epoetin on tumour growth was added to section 4.4:

"Effect on tumour growth
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 any type of malignancy. Two controlled clinical studies in which epoetins were administered to patients with various cancers including head and neck cancer, and breast cancer, have shown an unexplained excess mortality.
Platelet counts and haemoglobin level should also be monitored at regular intervals in cancer patients."

The CHMP also requested that the results from available studies on survival and progression-free survival in which epoetins were administered to patients with various cancers are reflected in section 5.1 as follows:

"~~Neither preclinical nor clinical investigations have shown any influence of epoetin beta on tumour progression~~…

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. There is insufficient information to establish whether the use of epoetin products have an adverse effect on time to tumour progression or progression free survival.

Two studies explored the effect of epoetins on survival and/or tumour progression with higher haemoglobin targets.

In a randomised placebo-controlled study using epoetin alfa in 939 metastatic breast cancer patients, study drug was administered to attempt to maintain haemoglobin levels between 12 and 14 g/dL. At four months, death attributed to disease progression was higher (6 % vs. 3 %) in women receiving epoetin alfa. The overall mortality was significantly higher in the epoetin alfa arm.

In another placebo-controlled study using epoetin beta in 351 patients with head and neck cancer, study drug was administered to maintain the haemoglobin levels of 14 g/dL in women and 15 g/dL in men. Locoregional progression free survival was significantly shorter in patients receiving epoetin beta. The results of this study were confounded by imbalances between the treatment groups, especially with regard to tumor localization, smoking status and the heterogeneity of the study population.

In addition, several other studies have shown a tendency to improved survival suggesting that epoetin has no negative effect on tumour progression."

As recommended by the CHMP, section 5.3 was also revised in line with 4.4 and 5.3 as follows:

"Carcinogenicity
~~*No effect of epoetin beta was observed on the proliferation of non haematological normal or malignant cells in vitro or transplantable tumours in vivo.*~~
A carcinogenicity study with homologous erythropoietin in mice did not reveal any signs of proliferative or tumourigenic potential".

Based on the analysis conducted, the CHMP recommended to remove the indication of prevention of anaemia in patients with solid tumour. The CHMP also emphasised during the procedure that the primary objective of the treatment with epoetins of cancer patients receiving chemotherapy was to alleviate anaemic symptoms rather than to correct Hb levels as such and recommended that this is clearly reflected in the indication. Finally, the CHMP agreed with the proposal of the MAH to further modify the cancer indication by removing the reference to platinum-based chemotherapy for patients with solid tumours. The indication in cancer patients was consequently amended as follows:

~~*"Prevention and t*~~*Treatment of* ***symptomatic*** *anaemia in adult patients with solid tumours*~~ *and treated with platinum-based chemotherapy prone to induce anaemia (cisplatin: 75 mg/m^2/cycle, carboplatin: 350 mg/m^2/cycle)*~~ ***receiving chemotherapy****."*

Treatment of ***symptomatic*** *anaemia in adult patients with multiple myeloma, low grade non-Hodgkin's lymphoma or chronic lymphocytic leukaemia, who have a relative erythropoietin deficiency and are receiving anti-tumour therapy. Deficiency is defined as an inappropriately low serum erythropoietin level in relation to the degree of anaemia."*

In the same variation procedure, section 4.8 was revised in order to update the incidence of thromboembolic events in cancer patients treated with NeoRecormon and to remove the statement on the uncertainty of the causal relationship between the occurrence of thromboembolic events and Neorecormon.