Product name: **ARANESP**
Procedure No. **EMEA/H/C/332/II/28**

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 for the treatment of anaemic cancer patients receiving chemotherapy were amended as detailed below.

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

"Haemoglobin level should not exceed 13 g/dl (8.1 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."

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:

"*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. 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."

In addition, the CHMP 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 to clearly reflect this in the indication as follows:

*"Treatment of **symptomatic** anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy."*

In the same variation procedure, "dyspnoea" has been included in section 4.8 of the SPC as an allergic manifestation of darbepoetin alfa use further to the assessment of PSUR 4 and 5.