European Medicines Agency
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QUESTIONS AND ANSWERS ON EPOETINS AND THE RISK OF TUMOUR GROWTH AND BLOOD CLOTS IN THE VEINS

The European Medicines Agency (EMEA) has reviewed the safety of epoetins used in cancer patients. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that there is a need to include a warning in the prescribing information for all epoetin-containing medicines stating that blood transfusions should be preferred in cancer patients with a reasonably long life expectancy.

What are epoetins?
Epoetins are copies of the natural substance erythropoietin, a hormone that is produced by the kidneys and stimulates the production of red blood cells from the bone marrow. Epoetin-containing medicines are used to treat anaemia (low red blood cell counts) in patients with cancer who are receiving chemotherapy and in patients with kidney problems. In these patients, anaemia can be caused by a lack of erythropoietin, or by the body not responding enough to the erythropoietin it has naturally. Epoetin-containing medicines are used to replace the missing hormone and increase red blood cell counts.

There are 12 medicines containing epoetins that are available on the market in the European Union. They may be authorised for use in both cancer and kidney patients, or only in kidney patients:

- epoetin-containing medicines that can be used in both cancer and kidney patients are: Eprex and Erypo (epoetin alfa), Aranesp and Nespo (darbepoetin alfa), NeoRecormon (epoetin beta), Retacrit and Silapo (epoetin zeta), and Abseamed, Binocrit and Epoetin Alfa Hexal (epoetin alfa);
- Mircera (methoxy polyethylene glycol-epoetin beta) and Dynepo (epoetin delta) can only be used in patients with kidney problems.

What is the issue with epoetins?
The European Medicines Agency (EMEA) is closely monitoring the safety of epoetin-containing medicines. In September 2007, the Agency finalised a full safety review of all epoetins, which has resulted in changes to the prescribing information for all the medicines, to ensure they are only used in patients whose anaemia is causing symptoms, such as weakness or a lack of energy. Epoetins should be used to raise the levels of haemoglobin (the red pigment in red blood cells) but only to between 10 and 12 g/dl[1]. The Agency also requested that the companies that make epoetin-containing medicines provide any new information on their products to the EMEA.

New information has now been provided to the EMEA. The information comes both from the published literature as well as from unpublished sources, and indicates that epoetins may be associated with an increased risk of 'venothrombolic events' (VTEs, blood clots in the veins) and with an increased risk of tumour progression, and shorter overall survival times, when used in cancer patients.

The information included:

- a meta-analysis (an analysis of the pooled results of a number of studies) on the risk of blood clots and death with epoetins, which was published in the Journal of the American Medical Association

[1] See here for full details.

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in February 2008[2]. It shows a small but significantly increased risk for overall death rates in patients receiving epoetins, as well as an increased frequency of VTEs, in comparison with placebo (dummy treatments) or standard care;
- a study in women with cervical cancer published in the journal Gynecologic Oncology in February 2008[3]. The study was stopped early because of concerns over the number of VTEs seen in the patients receiving epoetins;
- the interim results of an unpublished study carried out with darbepoetin alfa in women with breast cancer. These showed a small increase in the death rate in the patients receiving darbepoetin alfa. However the results are incomplete, as the full analysis is not yet available.

None of the additional information concerned patients being treated for kidney disease.

What action is the EMEA taking?

The Committee for Medicinal Products for Human Use (CHMP) and its Pharmacovigilance Working Party discussed the available information and its impact on the use of epoetin-containing medicines. The Committee also called on expert advice, convening a meeting of the 'oncology scientific advisory group', which brought together leading European experts specialised in cancer. The experts stated that in cancer patients with a reasonably long life-expectancy, the benefit of using epoetins to avoid blood transfusions does not balance the risks of tumour progression and shorter survival.

Based on the group's recommendation, the Committee agreed that the product information for all epoetins that are authorised for use in cancer patients should be updated to include a warning that transfusion should be the preferred method for correcting anaemia in cancer patients, especially those with a long life expectancy. The Committee also recommended that the companies who make epoetin-containing medicines should carry out, as a priority, additional studies to clarify the risks and benefits of epoetins used in the treatment of cancer patients as currently recommended. The CHMP will continue to review the safety of epoetin-containing medicines as additional data becomes available.

What are the consequences of the EMEA's action for patients and doctors?

- There are no consequences on the use of epoetin-containing medicines when they are used to treat anaemia in patients with kidney problems.
- Doctors who prescribe epoetin-containing medicines for the treatment of anaemia in cancer patients must remember that they should use them only in patients when their anaemia is causing symptoms and is having an impact on their state of health.
- Doctors are warned that blood transfusion is the preferred option for treating anaemia in cancer patients with a good prognosis. Epoetins should only be used when the benefit in terms of patient preference clearly outweighs the risk of the cancer getting worse.
- Patients who are receiving epoetin-containing medicines and who have concerns should talk to their doctor.

Are there any further steps?

The CHMP has asked the companies who make epoetin-containing medicines to implement these changes via a change (variation) to the marketing authorisations for these medicines.

[2] Bennett *et al*. Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. JAMA 2008, 299(8):914-924.

[3] Thomas *et al*. Phase III trial to evaluate the efficacy of maintaining hemoglobin levels above 12.0 g/dL with erythropoietin vs above 10.0 g/dL without erythropoietin in anemic patients receiving concurrent radiation and cisplatin for cervical cancer. Gynecol Oncol 2008, 108(2):317-325.