**MHRA Public Assessment Report**

# Epoetins for the management of anaemia associated with cancer: risk of tumour progression and mortality

November 2007

## EXECUTIVE SUMMARY

Epoetins are used to treat patients with cancer who develop anaemia after chemotherapy. Untreated anaemia may cause symptoms of fatigue, poor exercise tolerance, palpitations, rapid heart rhythm, shortness of breath, and, in severe cases, heart failure. In patients with cancer, severe symptoms of anaemia may lead to reduced tolerance to chemotherapy, or may necessitate a reduction in the dose of chemotherapy, which may negatively affect prognosis and survival. Aggressive anticancer chemotherapy may increase the risk of anaemia and its severity. The probability that a patient may need treatment for anaemia may therefore increase with aggressive anticancer chemotherapy.

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency that is responsible for ensuring that medicines and medical devices work and are acceptably safe. Evidence-based judgments underpin the Agency's work to ensure that the benefits to patients and the public justify the potential risks. The MHRA keeps the safety of all medicines—including epoetins—under continual review.

The Commission on Human Medicines (CHM) advises ministers on the quality, safety, and efficacy of medicines. In June 2007, the Commission assessed the safety of four epoetins that are authorised in the UK: epoetin alfa (Eprex); darbepoetin alfa (Aranesp); epoetin beta (NeoRecormon); and epoetin delta (Dynepo, but this product is not authorised for treatment of cancer-associated anaemia). The advice of CHM was fed into a Europe-wide review co-ordinated by the European Medicines Agency (Dynepo, Aranesp and NeoRecormon have centralised European licences). This Public Assessment Report summarises the data reviewed by CHM and summarises their recommendations.

Concerns about excess mortality associated with epoetins in the treatment of some patients with cancer were raised after publication in October 2003 of a randomised placebo-controlled trial of the effect of correction of anaemia with epoetin beta in patients with head and neck cancer who had had radiotherapy. The results of the study showed that patients treated with epoetin beta achieved correction of anaemia, but that local tumour progression and overall survival were statistically significantly worse after treatment with epoetin than with placebo. A second study compared epoetin alfa with placebo in the treatment of women with metastatic breast cancer who were receiving chemotherapy. The study was stopped prematurely because of higher mortality in the group treated with epoetin alfa.

European review of these data concluded that there was insufficient evidence to suggest that the balance of risks and benefits of epoetins was unfavourable in their authorised indications, under the conditions of use recommended in the Summaries of Product Characteristics (SPCs). However, the data provided a strong signal for a detrimental effect of epoetins on tumour progression and overall survival. Moreover, they highlighted an excess risk of venous thromboembolism in patients with cancer who were treated with epoetins to achieve haemoglobin concentrations in excess of those needed to correct anaemia. On the basis of this review, changes were made to all epoetin SPCs to reflect the findings of the two new studies. The SPCs were updated to: advise caution; amend the wording of the indication to treatment of patients with *symptomatic* anaemia; and limit the target haemoglobin concentration to 12 g/dL and the concentration that should not be exceeded to 13 g/dL. Marketing Authorisation Holders also produced risk-management plans to manage the apparent risk of epoetins in the treatment of patients with cancer.

After this regulatory action, a Cochrane review of epoetins in the management of anaemia associated with cancer was published in July 2006. This review includes data from 57 randomised controlled studies with 9353 participants, including the two studies

described above. The systematic review analysed evidence for haematological response, the need for red-blood-cell transfusion, changes in quality of life, tumour response, overall survival, and adverse events.

The survival meta-analysis in the systematic review provides no evidence to suggest that epoetins may improve overall survival, and none to suggest that epoetins may lead to reduced overall survival. The estimated hazard ratio was 1·08 (95% CI 0·99–1·18) in favour of the control group. On the basis of available data, it was not possible to identify a subgroup of patients that might have a higher risk compared with others of detrimental effects from epoetins. The review highlighted strong evidence to conclude that epoetins may increase the risk of thrombosis and related complications.

Further studies have since come to light that corroborate the signal to suggest a potential detrimental outcome in the management of anaemia in cancer. Five controlled studies have shown that epoetin treatment is associated with decreased overall survival, or increased risk of tumour progression, compared with controls. These studies are some of the largest controlled trials of epoetins in this indication (total 2833 patients). Point estimates for the hazard ratio for overall survival ranged from 1·25 to 2·47 in favour of the control group. An open label study (for which only preliminary data were available) found no difference in overall survival, but a statistically significantly increased risk of tumour progression. Two studies aimed to achieve target haemoglobin concentrations in excess of those recommended in the SPCs (ie, <13 g/dL), but the three other studies were mainly consistent with the target concentration recommended in the SPCs (about 12–14 g/dL). Two studies recruited patients who were receiving chemotherapy. Median progression-free survival and median time to death in patients treated with epoetin were estimated to be about half that of controls in two of the studies.

Epoetins that are authorised in the European Union (EU) for the treatment of anaemia associated with cancer are authorised only for patients who are receiving chemotherapy. For epoetin beta and darbepoetin alfa, treatment of *symptomatic* anaemia is specifically indicated. The dosing recommendations for all epoetins that are authorised for treatment of patients with cancer state that: treatment should start when haemoglobin concentration is 11 g/dL or less; haemoglobin concentration should not exceed 13 g/dL; and that the maximum rate of rise of haemoglobin concentration should not be greater than 2 g/dL per month.

The benefit attributed to epoetins for treatment of anaemia in patients with cancer with epoetins in order to obtain Marketing Authorisation was measured in terms of reduction in the number of blood transfusions and improvement in symptoms of anaemia (as assessed by Functional Assessment of Cancer Therapy [FACT]—fatigue score). Epoetins have not been shown to increase survival in patients with cancer.

Data from recent clinical trials show a consistent, unexplained excess mortality in patients with anaemia associated with cancer who have been treated with epoetins. Overall survival outcome in the studies could not be explained satisfactorily on the basis of different incidences of thrombosis and related complications between epoetins and controls. Some studies have included patients who meet the criteria in the authorised indications for epoetins. Given the number studies and the consistent outcomes, it is unlikely that their findings are due to chance.

The main serious risks associated with epoetins are due to the effects of increasing blood viscosity (ie, hypertension and venous thromboembolism), pure red-cell aplasia due to neutralising antibodies, a potential reduction in overall survival in patients with some tumours, and an increased likelihood of tumour progression. These risks must be matched against those associated with an alternative treatment—ie, blood transfusion—which carries a risk of acute fluid overload, immunological reactions (which may also lead

to red cell aplasia), infusion reactions, haemolysis, reduced resistance to postoperative infections, and transmission of blood-borne pathogens. Furthermore, the immunomodulatory effect of blood transfusion might reduce overall survival in patients with some tumours and increased the likelihood of tumour progression.

The Commission on Human Medicines has advised that further studies would be necessary to estimate the effect of epoetins on survival and tumour progression as well as the nature and extent of the benefit attributable to treatment of symptomatic anaemia associated with cancer in patients who are receiving chemotherapy. The Commission also advised that the available data do not enable with reasonable certainty the definition of a target range for haemoglobin concentration that has a consistently favourable balance of risks and benefits. However, no advantage has been shown to be associated with attaining a haemoglobin concentration in excess of 12 g/dL in patients with cancer. It should therefore not be necessary to exceed this concentration. The purpose of treatment with epoetins is to relieve symptoms of anaemia and to avoid the need for blood transfusion. The Commission advised treatment with epoetins should be appropriately adjusted when symptoms of anaemia have been adequately brought under control, irrespective of haemoglobin concentration. Symptoms of anaemia may be controlled at haemoglobin concentrations that are lower than those conventionally considered to be normal.

The Commission also advised that the evidence does not enable conclusions to be drawn about the management of patients who are receiving curative chemotherapy as distinct from those receiving palliative chemotherapy.

# 1 INTRODUCTION

Epoetins are used to treat patients with cancer who develop anaemia after chemotherapy. Untreated anaemia may cause symptoms of fatigue, poor exercise tolerance, palpitations, rapid heart rhythm, shortness of breath, and, in severe cases, heart failure. In patients with cancer, severe symptoms of anaemia may lead to reduced tolerance to chemotherapy, or may necessitate a reduction in the dose of chemotherapy, which may negatively affect prognosis and survival. Aggressive anticancer chemotherapy may increase the risk of anaemia and its severity. The probability that a patient may need treatment for anaemia may therefore increase with aggressive anticancer chemotherapy.

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The Commission on Human Medicines (CHM) advises ministers on the quality, safety, and efficacy of medicines. In June 2007, the Commission assessed the safety of four epoetins that are authorised in the UK: epoetin alfa (Eprex); darbepoetin alfa (Aranesp); epoetin beta (NeoRecormon); and epoetin delta (Dynepo, but this product is not authorised for treatment of cancer-associated anaemia). The advice of CHM was fed into a Europe-wide review co-ordinated by the European Medicines Agency (Dynepo, Aranesp and NeoRecormon have centralised European licences). This Public Assessment Report summarises the data reviewed by CHM to suggest an increased risk of tumour progression and reduced life expectancy in patients with some types of solid cancer after the use of epoetins to increase haemoglobin concentration.

**Table 1** shows the currently authorised indications for the four epoetins. Epoetin delta is authorised only for the treatment of anaemia associated with chronic renal disease in adults.

**Table 1: Authorised indications for epoetins authorised in the EU**

| | **Authorised indications in the EU** |
|---|---|
| **Epoetin alfa (Eprex)** | **Renal:**<br>• Treatment of anaemia associated with chronic renal failure in paediatric and adult patients on haemodialysis and adult patients on peritoneal dialysis<br>• Treatment of severe anaemia of renal origin accompanied by clinical symptoms in adults with renal insufficiency not yet undergoing dialysis<br>**Cancer:**<br>• Treatment of anaemia and reduction of transfusion requirements in adults receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma, and at risk of transfusion as assessed by the patient's general status<br>**Others:**<br>• To increase the yield of autologous blood from patients in a predonation programme<br>• To reduce exposure to allogeneic blood transfusions in adult non-iron deficient patients prior to major elective orthopaedic surgery, having a high perceived risk for transfusion complications |
| **Epoetin beta (Neorecormon)** | **Renal:**<br>• Treatment of anaemia associated with chronic renal failure in patients on dialysis<br>• Treatment of symptomatic renal anaemia in patients not yet undergoing dialysis<br>**Cancer:**<br>• Treatment of symptomatic anaemia in adult patients with non-myeloid malignancies receiving chemotherapy<br>**Others:**<br>• Prevention of anaemia of prematurity in infants with a birth weight of 750 g to 1500 g and a gestational age younger than 34 weeks<br>• Increasing the yield of autologous blood from patients in a pre-donation programme |
| **Darbepoetin alfa (Aranesp)** | **Renal:**<br>• Treatment of anaemia associated with chronic renal failure in adults and paediatric patients age 11 years or older<br>**Cancer:**<br>• Treatment of symptomatic anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy |
| **Epoetin delta (Dynepo)** | • Treatment of anaemia in adults with chronic renal failure |

## 2. EPOETINS FOR TREATMENT OF ANAEMIA ASSOCIATED WITH CANCER

### 2.1 Background

Concerns about the safety of epoetins in the treatment of some patients with cancer were raised after publication in October 2003 of a randomised placebo-controlled trial of the effect of correction of anaemia with epoetin beta in patients with head and neck cancer who were receiving radiotherapy.[1] The results of the study showed that patients treated with epoetin beta achieved correction of anaemia, but that local tumour progression and

overall survival were statistically significantly worse after treatment with epoetin than with placebo.

In February 2004, there was a European review of the available information for all epoetins that were authorised in the EU. The data reviewed comprised the above study[1] and a study[2] that compared the effect of epoetin alfa with that of placebo in the treatment of women with metastatic breast cancer who were receiving chemotherapy. The study was stopped prematurely on the advice of the Independent Data Monitoring Committee because of higher mortality in the group treated with epoetin alfa.

The review also considered: data from the Marketing Authorisation Holders (MAHs, including preclinical studies and clinical cancer studies); pooled analyses of cancer studies; subgroup analyses of cancer studies; spontaneous reports of cancer and cancer progression irrespective of the indication for treatment. Data supplied by the MAHs for thromboembolic events were also reviewed from: preclinical studies; published and unpublished clinical studies in patients with cancer; and spontaneous reports in patients treated for cancer.

The review concluded that there was insufficient evidence to suggest that the balance of risks and benefits of epoetins was unfavourable in their authorised indications, under the conditions of use recommended in the Summaries of Product Characteristics (SPCs). However, the data presented a strong signal for a detrimental effect of epoetins on tumour progression and overall survival, and also highlighted an excess risk of venous thromboembolism in patients with cancer who were treated with epoetins to achieve haemoglobin concentrations in excess of those needed to correct anaemia. On the basis of the review, the following changes were made to epoetin SPCs:

- Removal of statements that claimed there was no evidence of an effect of epoetins on tumour progression and survival

- Amendment of the indications to state explicitly that epoetins were to be used in patients with cancer only if they had *symptomatic* anaemia

- Haemoglobin concentration in the management of anaemia in patients with cancer was not to exceed 13 g/dL. Target haemoglobin concentration was to be 12 g/dL.

- Insertion of the following warning into section 4.4 of the SPC: "*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*."

- Insertion of the following passage about the state of knowledge at the time into section 5.1 of the SPC: "*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 of exogenous erythropoietin 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 tumour 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*."

MAHs produced risk-management plans to manage the apparent risk of epoetins in the treatment of patients with cancer.

Several published and unpublished studies have recently come to light that corroborate the signal presented by the first two studies.[1,2] The following sections of this report summarise the studies that suggest a detrimental outcome associated with epoetins in the management of anaemia in cancer.

## 2.2 Clinical studies in patients with cancer

### 2.2.1 Epoetin beta in patients with head and neck cancer given radiotherapy

This study was reported by Henke and colleagues.[1]

**Objectives**

To investigate whether correction of anaemia with epoetin beta could improve outcome of curative radiotherapy in patients with head and neck cancer.

**Trial design**

Multicentre, randomised, double-blind, placebo-controlled trial. Adults were eligible if they had histologically proven squamous-cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx, and if they were scheduled to undergo definitive radiotherapy or postoperative radiotherapy for advanced disease (ie, tumour stages T3, T4, or lymph-node involvement). Haemoglobin concentration was required to be lower than 120 g/L for women or lower than 130 g/L for men.

Patients were stratified according to tumour-resection status: postoperative irradiation of completely resected (ie, R0) tumour; postoperative irradiation of incompletely resected disease (ie, R1 or R2); or primary definitive radiotherapy. Patients were randomly assigned epoetin beta 300 IU/kg subcutaneously three times a week or placebo. Study drug was started 10–14 days before radiotherapy and continued throughout radiotherapy. Treatment was discontinued when target haemoglobin concentrations were achieved (ie, ≥140 g/L in women or ≥150 g/L in men), or when haemoglobin increased by more than 20 g/L within 1 week. Treatment resumed if haemoglobin concentration fell below the target concentration. Haemoglobin concentration, platelet counts, leucocyte counts, serum iron, transferrin, and ferritin were measured weekly during the treatment phase.

Patients were seen for first follow-up 6 weeks after completion of radiotherapy, and every 3 months thereafter. The primary endpoint of the study was locoregional progression-free survival, defined as time to locoregional tumour progression or death, whichever occurred first. Time to locoregional tumour progression and overall survival were also assessed. Tumour progression was assumed when tumour size increased by more than 25%.

Two interim analyses were planned, preserving a nominal p=0·048 in the final analysis for the level of statistical significance (only one analysis was actually performed). Study power was set at 80% to detect a 32% risk reduction for locoregional progression-free survival at 220 events. Primary analysis was done by intention-to-treat. Progression-free survival was analysed by use of Cox's proportional hazards model, cofactors for which were stratum and tumour stage (as assessed by American Joint Cancer Committee criteria). Differences were tested with the two-sided Wald $\chi^2$ test. Kaplan-Meier estimates and hazard ratios or relative risk with 95% CI were calculated.

**Results**

The study was conducted essentially according to the protocol. About 10% of patients in both groups had major protocol violations.

351 patients were enrolled, 180 of whom were allocated epoetin beta. About 85% of patients in both treatment groups were male. Median age in both treatment groups was about 57 years (range 35–87). Baseline characteristics of both treatment groups were similar for baseline haemoglobin concentration, tumour location, tumour stage, treatment stratum, and resection status. There were more current smokers in the epoetin-beta group than controls (66% *vs* 53%), and the range of serum erythropoietin concentrations in the epoetin-beta group was wider than in the placebo group (11–446 U/L *vs* 3–168); however, median concentration was the same in both groups (11 U/L).

Mean haemoglobin concentrations increased with epoetin beta treatment for up to 6 weeks and stabilised thereafter. Mean concentration after 4 weeks of treatment was 124 g/L for placebo and 148 g/L for epoetin beta.

**Table 2** shows the effect of epoetin beta on the study endpoints:

**Table 2: Effect of epoetin beta on the study endpoints (Cox's proportional hazards analyses adjusted for stratum and cancer stage)**

| | **Relative risk** | **95% CI** | | **p** |
|---|---|---|---|---|
| | | **Lower** | **Upper** | |
| **Intention to treat** | | | | |
| Locoregional progression-free survival | 1·62 | 1·22 | 2·14 | 0·0008 |
| Locoregional progression | 1·69 | 1·16 | 2·47 | 0·007 |
| Survival | 1·39 | 1·05 | 1·84 | 0·02 |
| **Radiotherapy correct** | | | | |
| Locoregional progression-free survival | 1·42 | 1·01 | 2·01 | 0·04 |
| Locoregional progression | 1·38 | 0·88 | 2·14 | 0·15 |
| Survival | 1·22 | 0·86 | 1·73 | 0·26 |
| **Per protocol** | | | | |
| Locoregional progression-free survival | 1·35 | 0·94 | 1·95 | 0·11 |
| Locoregional progression | 1·41 | 0·87 | 2·27 | 0·16 |
| Survival | 1·13 | 0·78 | 1·64 | 0·52 |

208 (59%) of 351 patients in intention-to-treat analyses had locoregional tumour progression or died during follow-up—92 in the placebo group and 116 in the epoetin-beta group. 79 and 64 patients, respectively, were censored (ie, alive at last follow-up in the study). The stage-adjusted and stratum-adjusted relative risk (RR) for locoregional progression-free survival suggested a poorer outcome for patients assigned epoetin beta compared with controls (1·62 [95% CI 1·22–2·14], p=0·0008; **table 2**), and the corresponding Kaplan-Meier estimate showed a median locoregional progression-free survival of 745 days for placebo compared with 406 days for epoetin beta (p=0·04).

**Table 3** shows the Kaplan-Meier estimates for outcomes of this trial:

**Table 3: Kaplan-Meier estimates**

| | **Epoetin beta** | **Placebo** | **p** |
|---|---|---|---|
| **Intention to treat** | | | |
| Median locoregional progression-free survival (days) | 406 | 745 | 0·04 |
| Median time to locoregional progression (days) | Not reached | 280 | 0·09 |
| Median survival (days) | 605 | 928 | 0·09 |
| **Radiotherapy stratum 1 (complete resection)** | | | |
| Median locoregional progression-free survival (days) | 1049 | 1152 | 0·90 |
| **Radiotherapy stratum 2 (partial resection)** | | | |
| Median locoregional progression-free survival (days) | 377 | 1791 | 0·001 |
| **Radiotherapy stratum 3 (definitive treatment)** | | | |
| Median locoregional progression-free survival (days) | 207 | 141 | 0·006 |
| **Radiotherapy correct** | | | |
| Median locoregional progression-free survival (days) | 551 | 795 | 0·41 |
| **Per protocol** | | | |
| Median locoregional progression-free survival (days) | 605 | 748 | 0·80 |

Subgroup analyses showed that epoetin beta was associated with a statistically significantly poorer outcome in patients younger than age 60 years (compared with older), in patients in whom haemoglobin concentration at baseline was higher than 110 g/L (compared with lower), and in patients who had advanced disease or cancer of the hypopharynx (compared with others). However, patients with cancer of the hypopharynx who were treated with epoetin beta were more commonly male, current smokers, had relapsed at baseline, and had stage IV disease compared with placebo-treated patients.

Overall, 89 (52%) patients in the placebo and 109 (61%) in the epoetin-beta group died; 119 (34%) patients in the two treatment groups died from cancer.

**Summary**

The study[1] shows that patients with head and neck cancer who were receiving curative radiotherapy and who were treated with epoetin beta to achieve haemoglobin concentrations of 140 g/L or higher in women or 150 g/L or higher in men had increased

local tumour progression, decreased progression-free survival, and decreased overall survival than did patients treated with placebo. Treatment groups seemed balanced at baseline, although there were marginally more smokers in the epoetin-beta group and the range of serum erythropoietin concentrations in the epoetin beta group was wider than in the placebo group.

The target haemoglobin concentrations in this trial were higher than those recommended in the SPCs for epoetins. The contribution of serious cardiovascular events to the shorter overall survival in the epoetin group cannot be determined from the available data, although there were more deaths from unspecified cardiac causes in the epoetin-beta group (10 patients) than in the placebo group (5 patients).

The same group of investigators attempted to correlate[3] progression-free survival with erythropoietin-receptor expression on tissue samples from the tumours of 154 patients that took part in the above study. Samples from 104 patients were positive for erythropoietin-receptor expression. Locoregional progression-free survival was lower in patients treated with epoetin beta who were positive for erythropoietin receptor expression compared with similar patients treated with placebo (RR 2·07 [95% CI 1·27–3·36]; p<0·01). Progression-free survival did not differ between placebo and epoetin-beta groups in patients with tumours that did not express erythropoietin receptors (RR 0·94 [95% CI 0·47–1·90]; p=0·86).

**Assessor's comments:** This retrospective study[3] of cancer tissue from participants in the survival study by Henke and colleagues[1] supports the hypothesis that expression of erythropoietin receptors on tumour cells may contribute to, or act as a marker for, a worse prognosis in terms of progression-free survival in patients with head and neck cancers who have been treated with epoetins. This hypothesis should be tested systematically in a prospective study. It would have been preferable if all participants in the study had been included in this assessment of the association between survival and receptor expression. Whether erythropoietin-receptor expression on other tumour types shows a similar association with survival is not known.

### 2.2.2 Darbepoetin alfa in patients with head and neck cancer given radiotherapy

An unpublished study (DAHANCA 10) was terminated prematurely and only a preliminary analysis is currently available. The study was one of four survival studies that are part of an ongoing pharmacovigilance programme for darbepoetin alfa in cancer treatment.

#### Objective

The DAHANCA 10 study was designed to test the hypothesis that maintenance of haemoglobin concentration between 14·0 g/dL and 15·5 g/dL using darbepoetin alfa would improve locoregional disease control in patients with head and neck cancer who were receiving primary curative radiotherapy.

#### Trial design

The study was an open-label, randomised comparison of radiotherapy alone and radiotherapy plus darbepoetin alfa in patients with squamous-cell cancer of the head and neck. The primary endpoint was locoregional progression of head and neck cancer. Darbepoetin alfa was given to maintain haemoglobin concentration between 14·0 g/dL and 15·5 g/dL, and was withheld when this upper concentration was exceeded. The study was designed to enrol 600 patients and was powered to detect a 12% difference in 5-year local control rate in a two-sided log-rank test.

**Results**

The preliminary interim analysis showed that 158 (33%) of 484 patients had locoregional progression of underlying disease. Interim analysis showed a 10% difference in 3-year locoregional control in favour of the group given radiotherapy alone (p=0·01), but no significant difference in survival (p=0·08). No differences in the incidence of distant metastasis or death from non-cancer causes were identified. The preliminary interim analysis showed no excess risk of serious adverse events associated with darbepoetin alfa.

After interim analysis, the DAHANCA 10 study group elected to terminate the enrolment of patients on the grounds that a better outcome for patients given darbepoetin alfa would be highly unlikely. 520 patients had been randomised. Follow-up of all patients will continue, to allow assessment of long-term efficacy and safety.

**Summary**

Full details of this study are not yet available. The MAH has made a commitment to obtain as much detail as possible and to obtain the results of the definitive analysis of the available study data from the DAHANCA 10 study group as soon as these become available.

The study shows that patients with head and neck cancer who were receiving curative radiotherapy and who were treated with darbepoetin alfa to achieve haemoglobin concentrations between 14 g/dL and 15·5 g/dL had increased local tumour progression than did patients given radiotherapy alone.

Assessor's comment: The target haemoglobin concentrations in this trial were higher than those recommended in the SPCs for epoetins. The contribution of serious cardiovascular events to the worse overall survival in the epoetin group cannot be determined from the available data, although the frequency of death from non-cancer causes were reported to have been similar in both treatment groups.

Epoetins are neither indicated for the treatment of patients with asymptomatic anaemia, nor for the treatment of patients with cancer who are receiving radiotherapy.

### 2.2.3 Darbepoetin alfa in patients with anaemia associated with cancer

A study sponsored by the MAH (study 20010103) is available only as an abstract to an oral presentation by J Glaspy and colleagues given at the 2007 annual meeting of the American Association of Cancer Research (http://www.abstractsonline.com/viewer/?mkey=%7BE3F4019C%2D0A43%2D4514%2D8F66%2DB86DC90CD935%7D; type "Glaspy" into the search field).

**Objective**

To assess the effect of darbepoetin alfa on the need for red-blood-cell transfusions in patients with malignant disease and anaemia who are not receiving chemotherapy or radiotherapy.

**Trial design**

The study was a randomised, double-blind, placebo-controlled assessment. To enter the study, patients were required to have a haemoglobin concentration of 11 g/dL or lower, active cancer, and to have had no myelosuppressive chemotherapy or radiotherapy in the

4 weeks preceding admission to the study or planned for the 16-week trial treatment interval. Patients were stratified according to: haemoglobin concentration on screening (<10 g/dL *vs* ≥10 g/dL); geographic region; blood transfusion in the 12 weeks before study entry; tumour type or treatment (chronic lymphocytic leukaemia *vs* low-grade lymphoma *vs* hormonal drugs or antibodies *vs* all other subjects); and Eastern Cooperative Oncology Group performance status (0–1 *vs* 2).

Darbepoetin alfa was given every 4 weeks at a dose of 6·75 mcg/kg; dose increase was not allowed. Darbepoetin alfa treatment was stopped if haemoglobin concentration exceeded 13 g/dL, and was restarted at a 25% lower dose when haemoglobin concentration fell below 12 g/dL. The dose of darbepoetin alfa was reduced by 25% if haemoglobin concentration exceeded 12 g/dL or if it rose by more than 1 g/dL in any 14-day interval. Blood transfusion was recommended when haemoglobin concentration was 8 g/dL or less.

The primary endpoint was the occurrence of red-blood-cell transfusions from week 5 to week 17.

371 patients who completed the study were eligible to enter an extension study (study 20010149) for a further 16 weeks of treatment (also double-blind). All patients will be followed for survival outcome for at least 2 years.

**Results**

Of the 989 patients who entered this study, 52% completed the 16-week treatment period. Mean baseline haemoglobin concentration was 9·5 g/dL for both treatment groups. There were more men in the darbepoetin alfa group than in the placebo group (56% *vs* 45%) and more patients who had received previous cytotoxic chemotherapy (75% *vs* 68%). Time since last chemotherapy was shorter for the darbepoetin alfa group than for the placebo group (274 days *vs* 320 days). The most common tumour types in the study were non-small-cell lung cancer (NSCLC, 19%), breast cancer (14%), and prostate cancer (10%).

176 transfusions occurred in the darbepoetin alfa group compared with 215 in the placebo group (adjusted hazard ratio for primary endpoint of week 5–17: 0·89 [95% CI 0·65–1·22]; hazard ratio for week 1–17: 0·92 [95% CI 0·69–1·21]).

The proportion of patients receiving a first blood transfusion between weeks 5 and 17 was a secondary endpoint. Fewer patients given darbepoetin alfa needed a first transfusion within this time window compared with placebo (18% *vs* 24%; Kaplan-Meier estimate for this difference –4·2% [95% CI –9·7 to 1·2]). Not all patients with a haemoglobin concentration that fell to 8 g/dL or less received a transfusion in this trial, the reasons for which have not been satisfactorily explained (although there were marked regional differences in whether patients with low haemoglobin concentration were transfused). The Kaplan-Meier estimate for the combined endpoint of patients receiving a first transfusion between weeks 5 and 17 and patients with a haemoglobin concentration that fell to 8 g/dL or less but who were not transfused was –6·5% (95% CI –12·4 to –0·5).

On-study deaths were reported in 94 (20%) of 470 patients in the placebo group and 136 (26%) of 515 patients in the darbepoetin alfa group. More deaths occurred because of complications related to the underlying cancer in the darbepoetin alfa group than in the placebo group. No difference was recorded in the frequency of death from cardiovascular or thromboembolic events (placebo 8%, darbepoetin alfa 10%).

Overall, 216 (46%) of 470 patients given placebo and 250 (49%) of 515 patients given darbepoetin alfa died on study or in long-term follow-up. A stratified Cox regression

analysis for overall survival gives a hazard ratio for overall survival of 1·25 (95% CI 1·04–1·51) in favour of placebo. This analysis gives a statistically non-significant hazard ratio when gender, previous chemotherapy or radiotherapy, and stage IV disease were included as factors (1·2 [95% CI 0·99–1·45]).

The MAH concluded that, given the failure to demonstrate efficacy and given the observed survival outcome, the balance of benefits and risks for epoetin treatment of patients with anaemia associated with cancer is at best neutral and may possibly be negative.

**Summary**

The available data from the study show that patients with cancer and a haemoglobin concentration 11 g/dL or less who received neither radiotherapy nor chemotherapy and who were treated with darbepoetin alfa to achieve haemoglobin concentrations between 12 g/dL and ≥13 g/dL had decreased overall survival compared with patients treated with placebo. The difference could not be accounted for on the basis of differences in the incidence of serious cardiovascular events, including thromboembolic events.

Some of the difference in the survival outcome may be explained by possible baseline imbalances in prognostic factors such as gender, stage IV disease, and chemotherapy or radiotherapy received before entry to the study. These factors were not planned to be included in the analysis model, but are derived from post-hoc exploratory analyses of the data.

### 2.2.4 Epoetin alfa in patients with metastatic breast cancer given chemotherapy

This study was reported by Leyland-Jones and colleagues.[2]

**Objective**

To assess overall survival and quality of life associated with maintenance of haemoglobin concentration in the range of 12 g/dL to 14 g/dL with epoetin alfa versus placebo in women with metastatic breast cancer who were receiving first-line chemotherapy.

**Trial design**

This double-blind, randomised, placebo-controlled, multicentre study recruited women with stage IV metastatic breast cancer who were scheduled to receive first-line chemotherapy (previous hormonal therapy for metastatic disease or cytotoxic therapy in the adjuvant setting was permitted). There was no upper or lower limit of haemoglobin concentration for inclusion. Eastern Cooperative Oncology Group (ECOG) performance status was required to be 0–2 and life expectancy 6 months or longer. Concurrent radiotherapy and hormonal therapy were permitted.

Patients were randomly assigned to receive 12 month's treatment with epoetin alfa 40 000 U subcutaneously once weekly or with placebo, irrespective of tumour progression and corresponding change in chemotherapy regimen. Randomisation was stratified by metastatic category (bone metastases only *vs* other measurable metastatic lesions *vs* other non-measurable metastatic lesions). Epoetin treatment was started when measured haemoglobin concentration was lower than 13 g/dL. The dose of epoetin was adjusted to maintain haemoglobin concentration between 12 g/dL and 14 g/dL.

Kaplan-Meier estimates of 12-month overall survival were calculated by treatment group. The primary treatment comparison was based on a log-rank test stratified by metastatic

category. HRs with 95% CI and p values were calculated, and Cox-model regression analysis was done with covariates, including age, menopausal status, measurable or non-measurable metastatic lesions, oestrogen-receptor–positive or oestrogen-receptor–negative status, and past chemotherapy.

**Results**

Administration of study drug was stopped early in accordance with a recommendation from the Independent Data Monitoring Committee because of higher mortality in the group treated with epoetin alfa. Enrolment had been completed with 939 patients (469 assigned epoetin alfa, 470 assigned placebo). 35 patients were randomly assigned to treatment but did not receive study drug—14 (3%) in the placebo group and 21 (4%) in the epoetin-alfa group. **Table 4** shows patient disposition.

**Table 4: Patient disposition**

| | **Epoetin alfa** | **Placebo** |
|---|---|---|
| **Randomised** | 469 | 470 |
| **Completed double-blind phase** | 361 | 357 |
| Alive at end of 12-month double-blind phase | 270 | 304 |
| Died during study within 12 months of randomisation | 91 | 53 |
| **Withdrew from double-blind phase prematurely** | 108 | 113 |
| Alive 12 months after randomisation | 51 | 51 |
| Died after withdrawal, but within 12 months of randomisation | 57 | 62 |

Patient demographics and malignancy characteristics were generally similar between groups. However, there were notable differences between groups in baseline ECOG performance status (poorer in the epoetin alfa group), time since initial diagnosis (shorter for the epoetin alfa group), and length of disease-free interval (shorter for the epoetin alfa group). Baseline haematological assessments were generally similar between groups, but more patients in the epoetin alfa group (14%) than in the placebo group (11%) were anaemic at baseline (ie, haemoglobin concentration 10·5 g/dL or less). The most common prestudy chemotherapy regimens and hormonal agents were similar between groups.

Analysis of interim data at the time of study cessation and discontinuation of study drug showed that 249 patients (138 [28%] in the epoetin alfa group and 111 [23%] in the placebo group) died within 12 months of randomisation (p=0·02 between groups). Final analysis for the intention-to-treat population (based on Kaplan-Meier estimates) showed a decreased 12-month overall survival in the epoetin alfa group compared with the placebo group (70% *vs* 76%; HR 1·37, p=0·01). Primary causes of death within 12 months attributed by the investigator were: disease progression (27% for epoetin alfa *vs* 22% for placebo); chemotherapy toxicity (1·7% *vs* 0·2%); and thrombovascular events (1·3% *vs* 0·6%). Most of the survival difference observed at 12 months was already present at 4 months (**table 5**).

**Table 5: Causes of death in patients who died within 4 months of randomisation (intention-to-treat analysis)**

| | **Epoetin alfa** n=469 | | **Placebo** n=470 | |
|---|---|---|---|---|
| | Number of patients | % | Number of patients | % |
| **Alive at 4 months** | 428 | 91·3 | 454 | 96·6 |
| **Died within 4 months** | 41 | 8·7 | 16 | 3·4 |
| **Cause of death** | | | | |
| **Disease progression** | 28 | 6·0 | 13 | 2·8 |
| **Chemotherapy toxicity** | 3 | 0·6 | 1 | 0·2 |
| **Thrombovascular event** | 5 | 1·1 | 1 | 0·2 |
| **Other** | 4 | 0·9 | 1 | 0·2 |
| **Missing (not known)** | 1 | 0·2 | 0 | 0 |

Cox-model regression analysis to estimate treatment effect after adjustment for demographic and prognostic factors showed significantly reduced 12-month survival for the epoetin alfa group (adjusted HR 1·36 [95% CI 1·05–1·75], p=0·02). Subgroup analyses of various patient and baseline disease characteristics did not convincingly identify any subgroup that could account for the difference in 12-month mortality between groups.

Overall incidence of thrombovascular events was slightly higher in the epoetin alfa group (16%) than in the placebo group (14%). 6 patients allocated epoetin alfa and 2 allocated placebo who received at least one dose of study drug died from a thrombovascular event: pulmonary embolism in six patients (five allocated epoetin alfa and one allocated placebo) and acute myocardial infarction in the other two patients (one allocated epoetin alfa and one allocated placebo).

**Summary**

The data from the study show that women with metastatic breast cancer who were receiving chemotherapy and who were treated with epoetin alfa to achieve haemoglobin concentrations between 12 g/dL and 14 g/dL had reduced overall survival compared with patients treated with placebo. There was a 6% difference between groups in survival at 12 months that favoured placebo (HR 1·37; p=0·01). After adjustment for known prognostic factors, the lower 12-month survival in the epoetin alfa group remained significant (HR 1·36, p=0·02).

The difference in survival was not confirmed by a difference in other disease outcomes such as time to disease progression or tumour response. The difference could not be completely accounted for by differences in the incidence of serious cardiovascular events, including thromboembolic events.

Haemoglobin concentration was maintained at 12–14 g/dL more effectively with epoetin alfa than with placebo, but most patients in both groups were not, and did not become, anaemic. Patients who died within 12 months of randomisation tended to have lower haemoglobin concentration throughout the study. Lower baseline haemoglobin concentration was associated with a worse prognosis for survival, but maintenance of haemoglobin concentration with epoetin alfa did not improve survival.

### 2.2.5 Epoetin alfa in patients with non-small-cell lung cancer given chemotherapy

This study was reported by Wright and colleagues.[4]

**Objective**

To investigate the effects of epoetin alfa treatment on the quality of life for patients with anaemia associated with advanced NSCLC.

**Trial design**

This double-blind, randomised, placebo-controlled, multicentre study recruited patients with unresectable locally advanced (ie, stage IIIa or IIIb), metastatic, or recurrent NSCLC. Haemoglobin concentration for inclusion was 12 g/dL or lower. Non-platinum-based chemotherapy was permitted because such palliative treatment in these patients is common. ECOG performance status was required to be 0–2 and life expectancy 3 months or longer.

Patients were randomly assigned to epoetin alfa 40 000 U subcutaneously once-weekly or to placebo for 12 weeks. Randomisation was stratified by baseline haemoglobin concentration (<10 g/dL *vs* 10–12 g/dL) and by presence or absence of palliative radiotherapy. The dose of study drug was adjusted to maintain haemoglobin concentration between 12 g/dL and 14 g/dL.

The primary outcome was change in FACT-An score (Functional Assessment of Cancer Therapy—Anaemia) from baseline to week 12. The required sample size was estimated as 150 patients per treatment group. However, the trial was terminated prematurely on the advice of the Data Safety Monitoring Committee because of evidence of higher mortality in the epoetin alfa group in an unplanned interim assessment that was done in the light of the results from the studies by Leyland-Jones and colleagues[2] and Henke and colleagues.[1]

**Results**

At the time of study termination, 70 patients had been randomised (33 to epoetin alfa, 37 to placebo). The groups were balanced at baseline for known prognostic factors and previous treatments.

At 12 weeks after the start of treatment there were few data available for assessment of change in FACT—An score (14 epoetin alfa, 20 placebo). The difference between treatment groups for the primary outcome was not statistically significant. Mean change in haemoglobin concentration from baseline was statistically significantly higher in the epoetin alfa group than in the placebo group at 4 weeks, 8 weeks, and 12 weeks after randomisation (**table 6**).

**Table 6: Haemoglobin concentration**

| | Epoetin alfa | | | Placebo | | |
|---|---|---|---|---|---|---|
| | n | Mean (g/dL) | Change from baseline (g/dL) | n | Mean (g/dL) | Change from baseline (g/dL) |
| **Baseline** | 33 | 10·3 | | 37 | 10·3 | |
| **4 weeks** | 27 | 11·8 | 1·45 | 33 | 10·3 | –0·07 |
| **8 weeks** | 18 | 11·8 | 1·50 | 23 | 10·7 | 0·35 |
| **12 weeks** | 14 | 12·4 | 2·06 | 20 | 10·5 | 0·21 |

At the time of study discontinuation, median time to death was shorter in the epoetin alfa group compared with the placebo group (63 days *vs* 129 days; HR 1·84 [95% CI 1·01–3·35], p=0·04).

In the final analysis 32 of 33 patients treated with epoetin alfa and 34 of 37 placebo-treated patients had died (**table 7**). The Kaplan-Meier curves for overall survival up to 60 weeks after randomisation showed that median time to death was shorter in the epoetin alfa group compared with the placebo group (68 days *vs* 131 days, p=0·04).

**Table 7: Causes of death**

| | Epoetin alfa (n=33) | | Placebo (n=37) | |
|---|---|---|---|---|
| | Number of patients | % | Number of patients | % |
| **Alive** | 1 | 3·1 | 3 | 8·1 |
| **Died** | 32 | 97·0 | 34 | 91·9 |
| **Cause of death** | | | | |
| **Disease progression** | 28 | 87·5 | 31 | 91·2 |
| **Pneumonia** | 1 | 3·1 | 1 | 2·9 |
| **Myocardial infarction** | 0 | 0 | 1 | 2·9 |
| **Renal failure** | 0 | 0 | 1 | 2·9 |
| **Hyponatraemia** | 1 | 3·1 | 0 | 0 |
| **Bowel perforation** | 1 | 3·1 | 0 | 0 |
| **Missing (not known)** | 1 | 3·1 | 0 | 0 |

Few thrombovascular events were reported in this study. A patient died from myocardial infarction in the epoetin alfa group. Unspecified thrombosis was reported in one patient treated with epoetin alfa (it is not clear whether this is the same patient that experienced myocardial infarction) and in two patients treated with placebo.

**Summary**

The data from the study show that patients with advanced NSCLC who were receiving non-platinum chemotherapy and who were treated with epoetin alfa for 12 weeks to achieve haemoglobin concentrations between 12 g/dL and 14 g/dL had decreased overall survival compared with patients treated with placebo. After adjustment for known prognostic factors up to 26 weeks after randomisation, the decreased survival in the epoetin alfa group remained significant (HR 2·47 [95% CI 1·05–5·83]). This difference could not be accounted for by differences in the incidence of serious cardiovascular events, including thromboembolic events. Haemoglobin concentration was maintained at 12–14 g/dL more effectively with epoetin alfa than with placebo.

### 2.2.6 Systematic review of epoetin treatment in cancer

Several systematic reviews have assessed epoetins in the management of anaemia in patients with cancer. However, only two[5,6] of the published reviews assessed tumour progression and survival. The most comprehensive of these two studies is a Cochrane review published in July 2006,[6] which is summarised here. This review included data from the studies by Henke and colleagues[1] and Leyland-Jones and colleagues.[2]

**Objective**

The review aimed to obtain evidence on the outcomes of the use of epoetin alfa, epoetin beta, or darbepoetin to prevent or alleviate anaemia in patients with malignant disease in

terms of haematological response, need for red-blood-cell transfusion, changes in quality of life, tumour response, overall survival, and adverse events.

**Method**

The review included randomised controlled trials that used epoetin alfa, epoetin beta, or darbepoetin alfa to treat or prevent anaemia in patients of any age with malignant disease. Trial participants were required to have had malignant disease diagnosed according to clinical and histological (or cytological) criteria, and were included irrespective of type or stage of disease or of any previous therapy. All study participants had to be anaemic, or at risk of becoming anaemic, from chemotherapy or radiotherapy (or both) or the underlying malignant disease. Epoetins could be given subcutaneously or intravenously, and had to be given for at least 4 weeks. Trials with fewer than 10 patients in each treatment group (or stratum where randomisation was stratified) were excluded. Studies that had been stopped early or suspended were included in the analysis.

**Results**

The review summarises evidence from 57 studies with 9353 participants. Duration of study drug ranged from 6 weeks to more than 20 weeks. **Table 8** summarises relevant patient characteristics.

**Table 8: Characteristics of the study populations**

| | Number of studies | Number of patients |
|---|---|---|
| **Mean haemoglobin concentration at baseline (g/dL)** | | |
| <10 g/dL | 22 | 3936 |
| 10–12 g/dL | 14 | 2141 |
| >12 g/dL | 10 | 1972 |
| Not available | 11 | 1404 |
| **Disease type** | | |
| Solid tumours only | 34 | 5330 |
| Haematological cancer | 9 | 1519 |
| Myelodysplastic syndrome | 2 | 153 |
| Solid tumours and haematological cancer | 11 | 2221 |
| Not reported | 1 | 130 |
| **Cancer treatment** | | |
| Platinum-free chemotherapy | 15 | 3388 |
| Platinum-based chemotherapy | 16 | 1757 |
| Platinum-free and platinum-based chemotherapy | 8 | 1752 |
| Radiotherapy or radiochemotherapy | 9 | 1250 |
| No anticancer therapy | 4 | 363 |
| Unspecified chemotherapy | 5 | 619 |
| **Age-group** | | |
| Adults | 55 | 8897 |
| Children | 2 | 456 |
| **Study drug** | | |
| Epoetin alfa | 40 | 6412 |
| Epoetin beta | 8 | 1664 |
| Epoetin alfa and epoetin beta | 1 | 50 |
| Darbepoetin alfa | 5 | 1080 |
| Unspecified | 3 | 147 |
| **Route of administration** | | |
| Subcutaneous | 54 | Not available |
| Intravenous | 2 | Not available |
| Subcutaneous and intravenous | 1 | Not available |

### Haematological response

For the meta-analysis, haematological response was defined as an increase in haemoglobin concentration of 2 g/dL or more, or an increase in haematocrit of 6% or more, unrelated to transfusion. For participants with a baseline haemoglobin concentration of 12 g/dL or less, haematological response was more frequent in participants who received epoetins compared with controls (RR 3·43 [95% CI 3·07–3·84]; 22 trials, n=4307).

### Blood transfusion

Use of epoetins significantly reduced the relative risk of red-blood-cell transfusions (0·64 [95% CI 0·60–0·68]; 42 trials, n=6510). There was some evidence that the effect size might be influenced by the nature of the underlying disease. On average, participants in the epoetin group received one unit of blood less than the control group (overall weighted mean difference –1·05 [95% CI –1·32 to –0·78]; 14 trials, n=2353). The control group received 3·34 units of blood on average.

### Quality of life

There was evidence to suggest that epoetins might improve quality of life: results showed an overall positive effect, which was unlikely to be due to chance. The size of this effect is impossible to estimate from the methods of analysis used.

### Overall survival

The meta-analysis of overall survival included data from 42 studies with 8167 participants. The estimated hazard ratio was 1·08 (95% CI 0·99–1·18) in favour of the control group. There was little heterogeneity between trials ($\chi^2$=44·04 [df=39], p=0·27, $I^2$=11·5%, and funnel-plot analysis p=0·35).

25 trials that assessed this endpoint assessed only solid tumours, 8 studies included only haematological malignancies, and 8 studies included both solid and haematological tumours; 1 study involved patients with myelodysplastic syndrome. Patients received chemotherapy with platinum in 16 studies and chemotherapy without platinum in 13 studies. 8 trials applied radiotherapy or radiochemotherapy. In 2 studies, cancer treatment was unspecified, and in 3 studies no anticancer therapy was used. In 20 studies, the average baseline haemoglobin concentration was below 10 g/dL, in 8 studies it was 10–12 g/dL, in 7 studies it was above 12 g/dL, and in 7 studies was not reported. All but one study recruited adults. Epoetin alfa or epoetin beta was assessed in 37 studies, and 5 studies assessed darbepoetin alfa.

There were no statistically significant differences in overall survival between subgroups for different tumour types, different treatments, epoetin alfa or epoetin beta versus darbepoetin alfa, duration of drug treatment, iron supplementation, and duration of follow-up. Statistically significant subgroup differences were recorded for different mean haemoglobin concentrations at baseline: HR for death 1·01 (95% CI 0·89–1·15) for studies with baseline haemoglobin concentration <10 g/dL (20 trials, n=3765); HR 0·98 (95% CI 0·82–1·16) for baseline haemoglobin concentration 10–12 g/dL (8 trials, n=1712); and HR 1·27 (95% CI 1·05–1·54) for baseline haemoglobin concentration higher than 12 g/dL (7 trials, n=1696). However, for 7 studies with 994 participants, data for baseline haemoglobin concentration was unavailable (HR for death for epoetin 1·63 [95% CI 1·07–2·49]). On exclusion of this subgroup from analysis, differences in haemoglobin concentration at baseline did not significantly affect overall survival (p=0·09).

### Tumour response

The researchers attempted to assess the proportion of patients who showed a complete tumour response, but the available data were inadequate for this purpose.

### Thomboembolic events

The meta-analysis of thromboembolic events included data from 35 studies with 6769 participants. The estimated relative risk was 1·67 (95% CI 1·35–2·06). There was no statistically significant heterogeneity between trials ($\chi^2$=26·52 [df=34], p=0·82, $I^2$=0%). Funnel-plot analysis showed significant asymmetry, suggesting that negative results (ie, no thrombotic event) had been under-reported.

21 trials that assessed this endpoint included only patients with solid tumours, 5 studies only haematological cancer, 2 studies myelodysplastic syndrome, and 7 studies both solid and haematological tumours. Patients received radiotherapy or radiochemotherapy (8 studies), chemotherapy with platinum (12 studies), chemotherapy without platinum (11 studies), and no anticancer therapy (4 studies). In 14 studies, the average baseline

haemoglobin concentration was below 10 g/dL, in ten studies it was 10–12 g/dL, in 7 studies it was more than 12 g/dL, and for 4 studies it could not be determined.

### Other adverse events

The systematic review also analysed risk of hypertension, bleeding and thrombocytopenia, skin reactions, and convulsions. Analyses suggested that only the risk of hypertension may be increased in patients treated with epoetins.

### Summary

The meta-analysis[6] provides no evidence to suggest that epoetin therapy may improve overall survival, and none to suggest that epoetin therapy may lead to reduced overall survival. On the basis of the available data, it was not possible to identify a subgroup of patients that might have a higher risk of detrimental effects as a result of epoetin therapy.

The survival meta-analysis does not include all recent studies that have shown decreased overall survival for epoetins in patients with cancer compared with placebo. The researchers who did the meta-analysis commented on the lack of concordance between more recent data from Henke and colleagues[1] and Leyland-Jones and colleagues[2] and those of older studies. Differing outcomes were, in their view, consistent with chance, but could be accounted for by the clinical heterogeneity in the studies (eg, in types of cancer, treatments for cancer, haemoglobin targets, and baseline haemoglobin concentrations).

These data provide strong evidence to conclude that treatment with epoetins may increase the risk of thrombosis or related complications.

## 3. NICE GUIDANCE

In March 2006, the National Institute for Health and Clinical Excellence (NICE) issued guidance for the use of epoetins for the treatment of anaemia induced by cancer treatment.[7] The NICE appraisal was based on much of the information reviewed in this report, and included a targeted systematic review and economic appraisal of the three epoetins authorised for treatment of anaemia associated with cancer treatment. The meta-analyses done as part of the assessment concluded that there was no survival advantage for patients treated with epoetins compared with controls. The hazard ratios for survival were similar to those estimated in the Cochrane systematic review.[6]

The NICE appraisal takes into account the degree of concordance between the way in which epoetins have been administered in survival trials and the recommended conditions of use stipulated in the SPCs for the authorised epoetins. This concordance was found to be poor. None of the trials included in the NICE assessment were unequivocally administered within the authorised indications given in the SPCs. In the absence of randomised controlled trials of epoetins within their licensed indications, the assessors grouped trials according to how closely their inclusion criteria and treatment protocols matched the products' licensed indications. 7 randomised controlled trials were identified as having trial populations, doses, and starting and target haemoglobin levels that were similar to those indicated in the SPCs. The combined HR for survival from these trials was 0·94 (95% CI 0·68–1·30). 5 trials were identified as having trial populations and doses that were similar to those indicated in the SPCs, although the starting and target concentrations of haemoglobin were moderately high. The combined HR for these trials was 0·96 (95% CI 0·83–1·11).

The relative risk of blood transfusion for all trials that reported data for the number of patients who received a transfusion was 0·63 (95% CI 0·58–0·67, fixed effects) in favour of epoetins. For this outcome, the test for heterogeneity was highly statistically significant (p=0·0001), suggesting that cancer type and cancer treatment may affect the numbers of patients that received red-blood-cell transfusions in the trials. Iron supplementation also seemed to confer a risk reduction.

For the overall amount of blood transfused, very little difference between intervention and control groups was reported (weighted mean difference –1·05 units [95% CI –1.32 to –0·78]).

For health-related quality of life, the NICE appraisal concluded that although some trials recorded positive results, overall quality of analyses was poor: outcomes were often inadequately reported and various assessment scales were used, limiting comparability and making general assessments of study quality difficult. Many trials did not use validated health-related quality-of-life measures. Fewer than half of the studies included in the NICE review were placebo-controlled, meaning that bias may have been introduced.

The NICE appraisal recommends that further research is needed to establish the effects of epoetins in the management of anaemia induced by cancer treatment on health-related quality of life (specifically utility scores), including effects on fatigue. Moreover, it concludes that research is needed to confirm the benefits and risks associated with epoetins in the management of anaemia induced by cancer treatment (specifically those related to mortality) and to identify subgroups (including those with different tumour types) for whom the possible risks may be acceptable.

The guidance given in the final appraisal determination is as follows:

Epoetins are recommended for use in the management of anaemia only as part of ongoing or new clinical trials that are constructed to generate robust and relevant data in order to address the gaps in the currently available evidence as outlined above. Patients currently receiving epoetins could experience loss of well-being if treatment is discontinued at a time they did not anticipate. Because of this, patients should have the option to continue therapy until they and their consultants consider it appropriate to stop.

## 4. RISK/BENEFIT OF BLOOD TRANSFUSION FOR ANAEMIA ASSOCIATED WITH CANCER

Untreated anaemia may cause symptoms of fatigue, poor exercise tolerance, palpitations, tachycardia, and shortness of breath. In severe cases, when cardiac output can no longer compensate for reduced oxygen-carrying capacity, anaemia may lead to heart failure. In patients with cancer, severe symptoms of anaemia may lead to reduced tolerance of chemotherapy, or may necessitate a reduction in the dose of chemotherapy, which may negatively affect prognosis and survival. Aggressive anticancer chemotherapy may increase the risk of anaemia and its severity. The probability that a patient may need treatment for anaemia may therefore increase with aggressive anticancer chemotherapy.

In a large European survey of about 15 000 patients with cancer, at enrolment 39% had haemoglobin below 12 g/dL, 10% had haemoglobin below 10 g/dL, and 1% had haemoglobin below 8 g/dL.[7] However, the proportion of patients with anaemia increased during treatment, especially during chemotherapy. The proportion also varied by tumour type—eg, it was substantially higher in patients who had lymphoma, myeloma, or gynaecological cancer than in those with other types of cancer.[7]

Standard care options for people with anaemia that has been induced by cancer treatment include adjustments to the cancer treatment regimen, iron supplementation, and blood transfusion. Most patients who become anaemic do not receive any treatment for anaemia, but blood transfusion is the conventional alternative to epoetins for the treatment of moderate to severe anaemia. Blood transfusion and epoetins are not necessarily used in exactly the same way to manage anaemia in patients with cancer. Data suggest that in the absence of symptoms of anaemia the threshold haemoglobin concentration for blood transfusion is usually 8 g/dL. The dose recommendations for all epoetins that are authorised for treatment of patients with cancer state that: treatment should start when haemoglobin concentration is 11 g/dL or less; haemoglobin concentration should not exceed 13 g/dL; and that the maximum rate of rise of haemoglobin concentration should not be greater than 2 g/dL per month.

The benefit of blood transfusion in the management of anaemia due to cancer, and many other indications, is not well documented in the literature.[6] Therefore, the balance of risks and benefits of blood transfusion in this indication is difficult to define. The complications of blood transfusion are well-known.[8–10] There is a global movement towards the adoption of increasingly conservative triggers for the prescription of blood and blood products, driven mainly by the risk of transfusion-transmitted infections.[8]

The main serious immediate complications of blood transfusion are transfusion reactions, acute haemolytic reactions, anaphylaxis, and circulatory overload (**table 9**). The main serious long-term complications of blood transfusion are transmission of blood-borne pathogens, transfusion-related acute lung injury, transfusion-associated graft-versus-host disease, transfusion-related immune modulation, systemic inflammatory response syndrome, and multiple organ failure.[8–10]

**Table 9: Complications of blood transfusion with red cells[7–9]**

| | Estimated incidence per unit transfused | Comments |
|---|---|---|
| **Acute complications** | | |
| Transfusion reactions | 1:100 | |
| Circulatory overload | Not available | |
| Severe anaphylaxis | 1:500 000 | Patients who are IgA-deficient who also have anti-IgA are at particular risk |
| Acute haemolytic reactions (ABO incompatibility) | 1:42 000 | 1:14 000 units estimated to be transfused in error. Acute haemolysis occurs only in the third of patients who do not receive group O blood or other serologically compatible red-cell transfusions despite ABO incompatibility. Incidence of fatal haemolytic reactions estimated to be 1:600 000 |
| **Long-term complications** | | |
| Transmission of blood-borne pathogens | | |
| Bacterial contamination (sepsis) | 1:500 000 | Usually *Yersinia enterocolitica*, Pseudomonas, or Serratia |
| Fatal sepsis | <1:1 000 000 | |
| Hepatitis B virus | 1:205 000 | The most frequent significant transfusion transmitted viral infection |
| Hepatitis C virus | 1:872 000 to 1:1 700 000 | Lowest rates estimated for blood screened with nucleic-acid testing |
| HIV 1/2 | 1:1 400 000 to 1:2 400 000 | Lowest rates estimated for blood screened with nucleic-acid testing |
| Human T-lymphotropic virus I/II | 1:514 000 to 1:2 993 000 | |
| Variant CJD | Not known | Probably extremely rare. 3 cases published in the UK to date |
| Other transmissible agents | Not available | West Nile virus; Chagas disease (*T cruzi*); babesiosis (*B microti*); malaria |
| Transfusion-related acute lung injury | 1:1323 to 1:5000 | Increasingly recognised cause of acute lung injury. Commonly fatal. Higher incidence estimates most likely reflect true incidence |
| Systemic inflammatory response syndrome (SIRS) | Not available | Dose-dependent increased risk of SIRS after trauma |
| Multiple organ failure | Not available | Blood transfusion is an independent risk factor for multiple organ failure |
| Transfusion-related immune modulation | All patients | Clinically significant immunosuppression, leading to increased risk of serious infection (especially postoperatively); risk is dose-dependent. Evidence that transfusion increases risk of tumour recurrence and metastasis |
| Transfusion-associated graft-versus-host disease | Rare | Rare, but usually fatal. Occurs when viable T-lymphocytes from a donor homozygous for a HLA haplotype are transfused to a recipient heterozygous for the same HLA haplotype. |

## 5. EPOETINS AND CANCER—CONCLUSIONS

Concerns about excess mortality associated with epoetins in the treatment of some patients with cancer were raised after publication in October 2003 of a randomised placebo-controlled trial of the effect of correction of anaemia with epoetin beta in patients with head and neck cancer who received radiotherapy.[1] The results of the study showed that patients treated with epoetin beta achieved correction of anaemia, but that local tumour progression and overall survival were statistically significantly worse after treatment with epoetin than with placebo. A second study[2] was reported that compared epoetin alfa with placebo in the treatment of women with metastatic breast cancer who were receiving chemotherapy. The study was stopped prematurely on the advice of the Independent Data Monitoring Committee because of higher mortality in the group treated with epoetin alfa.

European review of the available data concluded that there was insufficient evidence to suggest that the balance of risks and benefit of epoetins was unfavourable in their authorised indications, under the conditions of use recommended in the SPCs. However, the data reviewed provide a strong signal for a detrimental effect of epoetins on tumour progression and overall survival, and they also highlight an excess risk of venous thromboembolism in patients with cancer who are treated with epoetins to achieve haemoglobin concentrations in excess of those needed to correct anaemia. On the basis of this review, changes were made to all epoetin SPCs, which: described the findings of the two new studies;[1,2] advised caution; and contained amended wording of the indication to treatment of patients with *symptomatic* anaemia, to limit the target haemoglobin concentration to 12 g/dL, and to limit the concentration that should not be exceeded to 13 g/dL. MAHs also produced risk management plans to manage the apparent risk of epoetins in the treatment of patients with cancer.

After this regulatory action, a Cochrane review[6] of epoetins in the management of anaemia associated with cancer was published in July 2006. The review includes data from 57 randomised controlled studies with 9353 participants, including the two studies described above.[1,2] The systematic review analysed evidence for haematological response, need for red-blood-cell transfusion, changes in quality of life, tumour response, overall survival, and adverse events.

The survival meta-analysis in the systematic review gives no evidence to suggest that epoetin therapy may improve overall survival, and none to suggest that epoetin therapy may lead to reduced overall survival. The estimated hazard ratio was 1·08 (95% CI 0·99–1·18) in favour of the control group. On the basis of the available data, it was not possible to identify a subgroup of patients that might have a higher risk of detrimental effects as a result of epoetin therapy.

The researchers that completed the review[6] commented on the lack of concordance between the results from more recent studies by Henke and colleagues[1] and Leyland-Jones and colleagues[2] and those of older studies. The differing outcomes were, in their view, consistent with chance, but could also be accounted for by the clinical heterogeneity in the studies (eg, in types of cancer, treatments for cancer, haemoglobin targets, and baseline haemoglobin concentrations). The review highlighted strong evidence to conclude that treatment with epoetins may increase the risk of thrombosis and related complications.

Further studies have recently come to light that corroborate the signal to suggest epoetins may be associated with a detrimental outcome in the management of anaemia in patients with cancer. 5 controlled studies have associated epoetin treatment with

decreased overall survival, or a greater risk of tumour progression, than controls (**table 10**). The studies are some of the largest controlled trials that have been done with epoetins in this indication (total 2833 patients). 4 were double-blind, placebo-controlled studies, and 1 was an open-label trial. The types of tumour studied included many common tumours (eg, breast, lung, and head and neck). All authorised epoetins have been studied. Point estimates for the hazard ratio for overall survival ranged from 1·25 to 2·47 in favour of the control group. An open-label study for which only preliminary data are available found no difference in overall survival, but a statistically significantly increased risk of tumour progression. 2 studies aimed to achieve target haemoglobin concentrations in excess of those recommended in the SPCs (ie, <13 g/dL), but the 3 remaining studies were mainly consistent with the target concentration recommended in the SPCs (ie, about 12–14 g/dL). Two studies recruited patients who were receiving chemotherapy. Median progression-free survival and median time to death in patients treated with epoetin were estimated to be about half that of controls in two of the studies.

**Table 10: Summary details of clinical trials**

| | **Treatment** | **Design** | **Type of cancer** | **HR for overall survival (95% CI)** | **HR for tumour progression (95% CI)** |
|---|---|---|---|---|---|
| Henke et al[1] (n=351) | Epoetin beta | Double-blind placebo control | Squamous cancer of head and neck, patients given radiotherapy | 1·39 (1·05–1·84) | 1·69 (1·16– 2·47) |
| DAHANCA 10 (n=484) | Darbepoetin alfa | Open-label; control group received radiotherapy alone | Squamous cancer of head and neck, patients given radiotherapy | No difference | 1·1, p=0·01 |
| 20010103 (n=989) | Darbepoetin alfa | Double-blind placebo control | Various solid tumours, patients were not given radiotherapy or chemotherapy | 1·25 (1·04–1·51) | Not available |
| Leyland-Jones et al[2] (n=939) | Epoetin alfa | Double-blind placebo control | Metastatic breast cancer, patients given radiotherapy or chemotherapy | 1·36 (1·05– 1·75) | No difference |
| Wright et al[4] (n=70) | Epoetin alfa | Double-blind placebo control | Non-small-cell lung cancer, patients given non-platinum chemotherapy | 2·47 (1·05–5·83) | Not available |

The epoetins that are authorised in the EU for treatment of anaemia associated with cancer are authorised only for patients who are receiving chemotherapy. For epoetin beta and darbepoetin alfa, treatment of *symptomatic* anaemia is specifically indicated. Dose

recommendations for all epoetins that are authorised for treatment of patients with cancer state that: treatment should start when haemoglobin concentration is 11 g/dL or less; haemoglobin concentration should not exceed 13 g/dL; and that the maximum rate of rise of haemoglobin concentration should not be greater than 2 g/dL per month. These recommendations are consistent with treatment guidelines in this indication. Guidelines from the American Society of Clinical Oncology and the American Society of Hematology recommend epoetins as a treatment option for patients with a haemoglobin concentration of 10 g/dL who are receiving chemotherapy, and suggest that treatment may be useful for symptomatic or at-risk patients with a haemoglobin concentration of 10–12 g/dL. The US National Comprehensive Cancer Network guidelines recommend epoetins for the treatment of cancer-related or treatment-related anaemia in patients with a haemoglobin concentration of 11 g/dL.

The benefit attributed to treatment of anaemia with epoetins in patients with cancer in order to obtain Marketing Authorisation was measured in terms of reduction in the number of blood transfusions and improvement in symptoms of anaemia (as assessed by the FACT—fatigue score). Epoetins have not been shown to increase survival in patients with cancer.

Data from clinical trials (**table 10)** show a consistent, unexplained excess mortality in patients with anaemia associated with cancer who have been treated with epoetins. Overall survival outcome in the studies could not be explained satisfactorily on the basis of different incidences of thrombosis and related complications between epoetins and controls. Some studies have included patients who meet the criteria in the authorised indications for epoetins. Given the number of studies and the consistency of the outcome it is unlikely that the outcomes of these studies are due to chance.

The main serious risks associated with epoetins are due to the effects of increasing blood viscosity (ie, hypertension and venous thromboembolism), pure red-cell aplasia due to neutralising antibodies, a potential reduction in overall survival in patients with some tumours, and an increased likelihood of tumour progression. These risks must be matched against those associated with an alternative treatment—ie, blood transfusion—which carries a risk of acute fluid overload, immunological reactions (which may also lead to red cell aplasia), infusion reactions, haemolysis, reduced resistance to postoperative infections, and transmission of blood-borne pathogens (**table 9**). Furthermore, the immunomodulatory effect of blood transfusion might reduce overall survival in patients with some tumours and increased the likelihood of tumour progression.[8–10]

The Commission on Human Medicines advised that further studies would be necessary to estimate the effect of epoetins on survival and tumour progression as well as the nature and extent of the benefit attributable to treatment of symptomatic anaemia associated with cancer in patients who are receiving chemotherapy. The Commission also advised that the available data do not enable with reasonable certainty the definition of a target range for haemoglobin concentration that has a consistently favourable balance of risks and benefits. However, no advantage has been shown to be associated with attaining a haemoglobin concentration in excess of 12 g/dL in patients with cancer. It should therefore not be necessary to exceed this concentration. Epoetin treatment should relieve symptoms of anaemia and avoid the need for blood transfusion. The Commission advised that treatment with epoetins should be appropriately adjusted when symptoms of anaemia have been adequately brought under control, irrespective of haemoglobin concentration. Symptoms of anaemia may be controlled in some patients at haemoglobin concentrations that are lower than those conventionally considered to be normal.

The Commission also advised that the evidence does not enable conclusions to be drawn about the management of patients who are receiving primary curative chemotherapy, as distinct from those receiving palliative chemotherapy.

## 6. REFERENCES


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## 7. GLOSSARY

**Adjuvant**

A substance used alongside another to increase its activity

**Anaemia**

The circulation of too few red blood cells in the bloodstream, leading to reduced oxygen supply to tissues and organs

**Anaphylaxis**

A severe allergic reaction that leads to shortness of breath, wheezing, rash, and low blood pressure

**Allogeneic blood**

Blood from a donor that differs in genetic composition to that of the recipient

**Autologous blood**

Blood that is derived from the person that needs to receive it

**Baseline**

The time at the start of the study

**Chemotherapy**

Treatment of disease by use of chemical agents

**Chronic lymphocytic leukaemia**

A type of slowly progressing cancer of white blood cells

**Cytological**

Of cells

**Cytotoxic**

An substance that kills cells

**Erythropoietin**

A substance produced by the kidneys that regulates production of red blood cells

**Ferritin**

A protein that stores iron in the body

**First line**

The first type of treatment a person receives

**Graft-versus-host disease**

A condition that can arise after blood transfusion when cells present in blood of the donor mount an immune response against cells in the recipient

**Haematocrit**

A measure of the volume of blood that is filled by red blood cells

**Haematological**

Of blood

**Haemodialysis**

The process of filtering blood

**Haemoglobin**

The iron-containing component of red blood cells that carries oxygen around the body

**Haemolytic**

The break-up of blood cells

**Hazard ratio**

A method of measuring the risk of an event. A hazard ratio of more than 1 suggests an increased risk; a hazard ratio of less than 1 suggests decreased risk. Hazard ratios are usually accompanied by a 95% CI (confidence interval)—a statistical method of assessing the true difference between two groups: the range covered by this interval gives a 95% chance that the real difference between the two groups lies within this interval. If the 95% CI does not cross 1, then the hazard ratio is regarded as statistically significant

**Heterogeneity**

The extent of difference between two or more comparisons

**Histologically**

The appearance of the structure of cells and tissue under a microscope

**Hypertension**

High blood pressure

**Hyponatraemia**

A low level of sodium (salt) in the blood, leading to dehydration

**Hypopharynx**

Part of the **pharynx**

**IgA**

Immunoglobulin A: a molecule that forms part of the immune system

**Independent Data Monitoring Committee**

A group who has responsibility for continual analysis of an ongoing clinical trial and the results that are emerging from it

**Intention-to-treat analysis**

A method of analysing patients in a **randomised controlled trial**, who are assessed according to the treatment they were randomly allocated to receive, irrespective of whether they actually received this treatment. Such a method of analysis is thought to reflect findings that would occur with the treatment under investigation in real life

**Intravenous**

A method of giving treatment into a vein

**Kaplan-Meier estimates**

A measure of estimating survival of patients in a study over time since treatment

**Larynx**

The voicebox

**Leucocyte**

A white blood cell

**Local tumour progression**

Growth of cancerous tissue in the surrounding area

**Lymph node**

Part of the lymphatic system, which carries lymph (a substance that bathes tissues) around the body. The lymph nodes prevent foreign particles from entering the bloodstream

**Lymphoma**

A type of cancer of the blood

**Marketing Authorisation Holders**

A company that holds a licence to market a medicine

**Mean**

An average, calculated by dividing the sum of all values by the total number of values

**Median**

An average: the middle value of a range of values in a sample

**Meta-analysis**

A study that combines the results from several similar clinical trials that asked the same study question and applies new statistical analysis

**Metastatic**

Cancer that has spread beyond a primary site in the body

**Multiple myeloma**

A type of cancer of the bone marrow

**Myelodysplastic syndrome**

A disorder characterised low blood-cell counts due to defective bone-marrow cells

**Myeloid**

A term assigned to some types of white blood cells

**Myocardial infarction**

Injury to heart muscle as a result of reduced oxygen supply, leading to a heart attack

**Neutralising antibodies**

Cells of the immune system that help the body to fight infection

**Nucleic acid**

The component of DNA

**Oestrogen-receptor positive/negative**

Some breast tumours may express molecules on their surface that allow the hormone oestrogen to bind (positive), whereas others do not (negative)

**Open label study**

A study in which patients and healthcare professionals who are involved know the treatment to which the patients have been assigned (compare with a blinded study).

**Oropharynx**

The area of the throat at the back of the mouth

**Palliative**

Treatment that does not intend to cure, but to relive symptoms

**Peritoneal dialysis**

A particular type of kidney dialysis that runs dialysis fluid through the stomach

**Per-protocol analysis**

A method of analysing patients in a **randomised controlled trial**, who are assessed according to the treatment they actually received. For some patients, this treatment might differ from the one that they were randomly assigned during planning of the study (contrast with **intention-to-treat analysis**)

**Pharmacovigilance**

The monitoring of a medicine, particularly its safety, after it has received a license

**Placebo**

A dummy treatment (eg, a sugar pill) given to a group of patients in a **randomised controlled trial**

**Platelet**

A type of blood cell that has an important role in blood clotting

**Platinum**

A substance that is an active agent in some types of **chemotherapy** that kills cancer cells

**Primary endpoint**

The main question that a **randomised controlled trial** aims to answer

**Progression-free survival**

The time during which cancer does not progress in a patient after treatment

**Prospective**

A study in which people are recruited and subsequently followed over time

**Pulmonary embolism**

A blood clot in the lungs

**p value**

A measure of the statistical probability of an event occurring by chance. Usually, a p value of less than 0·5 suggests the event is statistically significant and did not occur by chance, whereas a p value of more than 0.5 suggests the event is not statistically significant and arose by chance

**Radiochemotherapy**

Treatment of cancer with a combination of **radiotherapy** and **chemotherapy**

**Radiotherapy**

Treatment of cancer by use of radiation, which destroys cancer cells

**Randomised placebo-controlled trial**

A study technique, regarded as robust, in which participants are enrolled onto the study and randomly assigned a treatment or treatment technique. In a **placebo** controlled trial, some patients are allocated the drug or technique of interest, whereas some are allocated **placebo** as a control group to identify the effects of the drug of interest. In a double-blind study, neither the trial participants nor the trial investigators are aware of who has been assigned to a particular treatment group, thus minimising bias

**Red-blood-cell transfusion**

The introduction of red blood cells into the bloodstream for those who are deficient (ie, anaemic)

**Red-cell aplasia**

A lack of production of red blood cells

**Relative risk**

A measure of risk for one group compared with another (eg, risk for patients given epoetin compared with those given **placebo**). A relative risk of more than 1 suggests an increased risk; a relative risk of less than 1 suggests decreased risk. Relative risks are usually accompanied by a 95% CI (confidence interval)—a statistical method of assessing the true difference between two groups: the range covered by this interval gives a 95% chance that the real difference between the two groups lies within this interval. If the 95% CI does not cross 1, then the hazard ratio is regarded as statistically significant

**Renal**

Of the kidneys

**Resected**

Surgical removal of body tissue

**Risk-management plans**

A document submitted by Marketing Authorisation Holders to drug regulatory authorities, which summarises: the known (and unknown) safety profile of a medicine; current and planned measures to monitor safe and effective use of a medicine; and the proposed strategies to ensure minimum to risk to the public from the medicine

**Sepsis**

Serious infection of the blood (eg, bacterial infection)

**Squamous-cell carcinoma**

A type of cancer

**Stratified/stratification**

A method of separating patients in a clinical trial into groups on the basis of their characteristics

**Subcutaneously**

A method of giving a medicine under the skin

**Summaries of Product Characteristics**

Detailed information that accompanies any licensed medicine. The Summary of Product Characteristics details the composition, clinical characteristics, pharmacological properties, pharmaceutical characteristics

**Systematic review**

An overview and appraisal of the current literature on a topic

**Systemic inflammatory response syndrome**

The mounting of an inflammatory response by the whole body to an infection; a serious medical condition that can lead to multiple organ failure

**Tachycardia**

A rapid heart rhythm

**Thrombocytopenia**

Decreased number of **platelets** in the bloodstream

**Thrombosis/thromboembolic**

Events leading, or related, to a blood clot

**T-lymphocytes**

A type of white blood cell that has an important role in the body's immune system

**Transferrin**

A protein that carries iron in the bloodstream

**Venous thromboembolism**

A blood clot in a vein