

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Epoetin alfa, epoetin beta and darbepoetin alfa for cancer treatment-induced anaemia

This guidance does not cover the use of erythropoietin analogues (epoetin alfa, epoetin beta and darbepoetin alfa) in the management of cancer-related anaemia that is not induced by cancer treatment (chemotherapy or radiotherapy).

During this appraisal the regulatory health authorities have conducted reviews into the safety of erythropoietin analogues. This guidance was produced taking the conclusions of those reviews into consideration, and should be read in conjunction with the reports published by the regulatory health authorities.

1 Guidance

- 1.1 Erythropoietin analogues are not recommended for routine use in the management of cancer treatment-induced anaemia, except in the circumstances described below.
- 1.2 Erythropoietin analogues are recommended in combination with intravenous iron as an option for the management of cancer treatment-induced anaemia in women receiving platinum-based chemotherapy for ovarian cancer who have symptomatic anaemia with a haemoglobin level of 8 g/100 ml or lower.
- 1.3 Erythropoietin analogues in combination with intravenous iron may be considered for people who cannot be given blood transfusions and who have profound cancer treatment-related anaemia that is likely to have an impact on survival.

- 1.4 In the circumstances outlined in 1.2 and 1.3, the erythropoietin analogue with the lowest acquisition cost should be used.
- 1.5 People who are currently being treated with erythropoietin analogues for the management of cancer treatment-related anaemia but who do not fulfil the criteria in 1.2 and 1.3 should have the option to continue their therapy until they and their specialists consider it appropriate to stop.

2 Clinical need and practice

- 2.1 Anaemia is defined as a reduction of haemoglobin concentration, red cell count or packed cell volume to below normal levels. The US National Cancer Institute considers normal haemoglobin concentrations to be 14–18 g/100 ml (men) and 12–16 g/100 ml (women). The World Health Organization definition states that anaemia should be considered to exist in adults whose haemoglobin concentration is lower than 13 g/100 ml (men) or 12 g/100 ml (women).
- 2.2 Anaemia in people having treatment for cancer can be caused by one or more factors associated with the cancer itself or with the treatment. Cancer can cause anaemia through mechanisms that are unrelated to treatment. For example, infiltration of the bone marrow by cancer cells can impair red blood cell production. Reduced appetite associated with cancer can lead to anaemia through nutritional deficiencies (particularly of iron and folate). Other mechanisms include blood loss into or from tumours, and cancer-associated kidney damage, which leads to reduced production of the hormone erythropoietin. Cancer treatment can also suppress the production of red blood cells in the bone marrow. This is usually temporary, but cumulative damage can occur over several chemotherapy cycles. Some cancer therapies are considered more likely to cause anaemia than others.

- 2.3 Anaemia is associated with many symptoms, all of which affect quality of life. These symptoms include dizziness, shortness of breath on exertion, palpitations, headache and depression. Severe fatigue is perhaps the most commonly reported symptom and can lead to an inability to perform everyday tasks. However, fatigue in people with cancer can also have other causes (for example, the disease itself, chemotherapy, radiotherapy, anxiety or depression).
- 2.4 Many people are anaemic when cancer is diagnosed, before any cancer treatment starts. The degree of anaemia caused by treatments such as chemotherapy often fluctuates depending on the nature of the treatment and the number of courses administered, but is typically at its worst 2–4 weeks after chemotherapy is given. Once cancer treatments are stopped, a period of 'normalisation' is likely, during which the haemoglobin may return to pretreatment levels.
- 2.5 In a large European survey of almost 15,000 people with cancer, at enrolment 39% had haemoglobin levels below 12 g/100 ml, 10% had levels below 10 g/100 ml and 1% had levels below 8 g/100 ml. However, the proportion of people with anaemia increased during treatment, particularly during chemotherapy. The proportion also varied according to tumour type (for example, it was substantially larger in people who had lymphoma/myeloma and gynaecological cancers than in those with other types of cancer).
- 2.6 Options available for the management of cancer treatment-induced anaemia include adjustments to the cancer treatment regimen, iron supplementation and blood transfusion. The majority of people who become anaemic do not receive any treatment for their anaemia, but those who become moderately or severely anaemic are usually given blood transfusions.

- 2.7 There are several concerns about the use of blood transfusions, in particular the limited supply of blood. Other concerns include alloimmunisation after a first blood transfusion and the possibility of giving incorrectly matched blood. There are also potential risks of introducing a serious infection such as hepatitis C or HIV, although donations are screened to minimise these risks.

3 The technologies

- 3.1 Erythropoietin is a glycoprotein hormone, which is produced mainly in the kidney and is responsible for regulating red blood cell production. Erythropoietin for clinical use is produced by recombinant DNA technology.
- 3.2 Epoetin alfa (Eprex, Janssen-Cilag) and epoetin beta (NeoRecormon, Roche) are recombinant erythropoietin analogues, each consisting of 165 amino acids in almost identical sequences to the native protein. Darbepoetin alfa (Aranesp, Amgen) is a hyperglycosylated derivative of epoetin. It has a longer half-life and therefore may be administered less frequently than epoetin.
- 3.3 Epoetin alfa has UK marketing authorisation for the treatment of anaemia and for the reduction of transfusion requirements in adults receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma, who are at risk of transfusion as assessed by their general status. It is administered to people with anaemia (haemoglobin 11 g/100 ml or lower) with the aim of achieving a target haemoglobin concentration of approximately 12 g/100 ml. The recommended initial dosage is 150 IU/kg body weight given by subcutaneous injection three times a week. See the summary of product characteristics (SPC) for further details.
- 3.4 Epoetin beta has UK marketing authorisation for the treatment of symptomatic anaemia (haemoglobin 11 g/100 ml or lower) in adults

- 3.5 Darbepoetin alfa has UK marketing authorisation for the treatment of symptomatic anaemia (haemoglobin 11 g/100 ml or lower) in adults with non-myeloid malignancies who are receiving chemotherapy. The recommended initial dosage is 6.75 micrograms/kg body weight given by subcutaneous injection once every 3 weeks. Alternatively, 2.25 micrograms/kg can be given once a week (see the SPC for further details).
- 3.6 Erythropoietin analogues (epoetin alfa, epoetin beta and darbepoetin alfa) are an addition to, rather than a replacement for, existing approaches to the management of anaemia induced by cancer treatment. Blood transfusion, in particular, may still be needed.
- 3.7 There is uncertainty about the potential side effects of erythropoietin analogues in people with anaemia who are receiving treatments for cancer. The European Medicines Agency (EMA) has recently reviewed the safety of erythropoietin analogues based on new data from both published and unpublished studies. These studies suggest an increased risk of serious cardiovascular complications in people with chronic renal failure and a possible effect on tumour progression in people with cancer. An earlier safety review by the EMA resulted in revised dosing recommendations for people receiving chemotherapy and in new safety warnings regarding possible stimulating effects on tumour progression. For full details of side effects and contraindications, see the SPCs.

- 3.8 The cost of a course of treatment with the least expensive of the three available erythropoietin analogues is approximately £2250–£4500 (excluding VAT; 'British national formulary' [BNF] edition 54). This excludes the associated administration costs, and assumes a mean body weight of 70 kg and that erythropoietin analogue treatment is given in the context of a 4-weekly chemotherapy regimen lasting for three to six courses. Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B).

4.1 *Clinical effectiveness*

- 4.1.1 The systematic review in the assessment report was an update of an earlier systematic review published by the Cochrane Collaboration. The assessment report included a total of 46 randomised controlled trials (RCTs); 27 were related to the use of epoetin alfa, 10 to the use of epoetin beta and five to the use of darbepoetin alfa. A further four RCTs either assessed the use of two different erythropoietin analogues within the same study or did not state which product was being evaluated.
- 4.1.2 All RCTs compared the use of erythropoietin analogues plus supportive care (including the use of blood transfusions) with supportive care alone. The types of malignancy within and across each study varied (for example, solid, haematological or mixed). Cancer therapies were chemotherapy (with or without platinum) or radiotherapy, or a combination of the two. Most of the trials stated that they included people whose haemoglobin was below a certain threshold level. The highest threshold for inclusion in a study was 16 g/100 ml and the lowest was 10 g/100 ml. The mean baseline

haemoglobin level at the time of randomisation ranged from 8.6 to 11.5 g/100 ml.

- 4.1.3 The pooled (fixed effects) relative risk (RR) for haematological response (defined as an increase in haemoglobin level of at least 2 g/100 ml) reported by the Assessment Group was 3.40 (95% confidence interval [CI] 3.01 to 3.83) in favour of erythropoietin analogue therapy, with little evidence of statistical heterogeneity. Typically, 50% of people treated with erythropoietin analogues experienced a haematological response.
- 4.1.4 The meta-analysis in the assessment report showed a weighted mean difference in overall change in haemoglobin concentrations, between intervention and control arms, of 1.63 g/100 ml (95% CI 1.46 to 1.80) in favour of erythropoietin analogue therapy.
- 4.1.5 The pooled RR for receiving blood transfusion across all trials reporting data on the number of people requiring a blood transfusion was 0.63 (95% CI 0.58 to 0.67, fixed effects) in favour of erythropoietin analogue therapy. For this outcome, the test for heterogeneity was highly statistically significant ($p = 0.0001$) and indicated that the type of malignancy and the type of therapy may influence the number of people receiving red blood cell transfusions.
- 4.1.6 In terms of the overall amount of blood transfused, a statistically significant difference, although small in absolute terms, between intervention and control arms was reported (weighted mean difference -1.05 units; 95% CI -1.32 to -0.78) in favour of erythropoietin analogue therapy.
- 4.1.7 For the outcome of survival, data were available from a total of 28 trials. Of these, 19 had been included in the original Cochrane review in which the hazard ratio (HR) associated with survival was

0.84 (95% CI 0.69 to 1.02) in favour of erythropoietin analogues. A single trial with positive results in favour of erythropoietin analogues contributed more than half of the results included in the original Cochrane review. The nine trials that have been reported since the publication of the original review suggest less benefit and, when analysed as a group, produced a HR for survival of 1.15 (95% CI 1.00 to 1.32) in favour of the control arm. Combining the data from all 28 trials produced a HR of 1.03 (95% CI 0.88 to 1.21) in favour of the control arm. However, there was considerable clinical heterogeneity within the studies in terms of the site of cancer, setting, dose and comparator.

- 4.1.8 Given this heterogeneity and the difference between the HR from the meta-analysis of all 28 trials (HR = 1.03) and that from the original Cochrane review of 19 trials (HR = 0.84), the Assessment Group was asked to conduct a meta-analysis on survival including only studies that used the erythropoietin analogues within their licensed indications. Studies were assessed based on a checklist of criteria derived from the SPC for each product (as at 24 November 2005). Two researchers working independently applied the criteria to each of the 28 RCTs included in the Assessment Group's meta-analysis. Application of the method suggested by Altman for inter-rater reliability indicated that there was good agreement between the two researchers (kappa = 0.74, 95% CI 0.64 to 0.84). The results of this exercise indicated that in none of the studies included in the Assessment Group's original meta-analysis of all 28 trials were erythropoietin analogues used unequivocally within the terms specified in the SPCs.
- 4.1.9 Change in health-related quality of life (HRQoL) was reported in fewer than half of the RCTs included in the Assessment Group's review of the clinical evidence base. Some positive results in favour of treatments were found. However, there are some methodological

concerns regarding these results because fewer than half of the studies included were placebo controlled. Outcomes were often inadequately reported and did not use validated HRQoL measures, which limited study comparability.

- 4.1.10 The Assessment Group conducted further searches and, if applicable, synthesised the results of identified studies to assess the clinical effectiveness of erythropoietin analogues:
- in different subgroups (people with any type of cancer receiving platinum-based chemotherapy, women with ovarian cancer receiving platinum-based chemotherapy, and people unable to receive blood transfusions) and
 - when used in association with intravenous iron supplementation.

4.1.11 In the subgroup analysis of people with any type of cancer who received platinum-based chemotherapy, the pooled estimates for haematological response outcomes (haematological response, haemoglobin concentration change, percentage of people receiving blood transfusions, and number of units of blood transfused), derived from trial-level and subgroup data within trials, showed a statistically significant effect for erythropoietin analogue therapy. However, of these outcomes, only the percentage of people receiving blood transfusions and the number of units transfused were statistically significantly lower in those treated with platinum-based chemotherapy than in those who had not received platinum-based chemotherapy. The HR for survival in the platinum-treated group was 0.97 (95% CI 0.84 to 1.11) for erythropoietin analogues compared with the control group. Twelve potentially relevant studies (of which five included people receiving platinum-based chemotherapy and measured survival) were not considered in the survival analysis because no subgroup data were available.

HRQoL data in the subgroup of people receiving platinum-based chemotherapy did not allow any relevant conclusions to be drawn.

4.1.12 In the subgroup analysis of women with ovarian cancer who received platinum-based chemotherapy, the pooled estimates for haematological response outcomes, derived from trial-level and subgroup data of studies, showed a statistically significant effect for erythropoietin analogue therapy. However, these results were not statistically significantly different from the results for the subgroup with other (non-ovarian) cancers who had also received platinum-based chemotherapy. Results suggested that treatment with erythropoietin analogues had a greater effect on tumour response in people with non-ovarian cancer than in women with ovarian cancer (receiving platinum-based chemotherapy). There was a suggestion of a greater survival benefit in women with ovarian cancer receiving platinum chemotherapy (HR = 0.71, 95% CI 0.44 to 1.14) than in people with other types of cancer (HR = 0.97, 95% CI 0.83 to 1.14), but this difference was not statistically significant. Moreover, in none of the subgroups did the results statistically significantly favour the erythropoietin analogue therapy. Nine potentially relevant studies (of which five included a mixed population with ovarian and non-ovarian cancers receiving platinum-based chemotherapy, and measured survival) were not considered in the analysis of this survival outcome because no subgroup data were available. Seven studies measuring HRQoL using various measurement methods were identified, but no statistically significant difference was reported between women with ovarian cancer treated with platinum and people treated with platinum for other types of cancer.

4.1.13 No trials were found that investigated the effectiveness of erythropoietin analogues in a population unable to receive blood transfusions. A literature search was performed to try to establish

the usual progression of haemoglobin levels in people unable to receive blood transfusions, but no relevant studies were identified. The Assessment Group concluded that there were no empirical data that would allow a legitimate estimation of either the effect of erythropoietin analogues in people who cannot receive blood transfusions or the range of haemoglobin levels in this group.

- 4.1.14 Analysis of the trials that included people receiving erythropoietin analogues and iron supplementation showed that the administration of supplemental intravenous iron resulted in a statistically significantly higher haematological response (that is, a higher proportion of people had an increase in haemoglobin concentration of 2 g/100 ml or greater, or achieved a haemoglobin concentration of 12 g/100 ml, without transfusion) and greater absolute change in haemoglobin concentration. In addition, where reported, there was a reduction in the RR for receiving blood transfusions. However, the Assessment Group noted that these effects differed in magnitude across trials. It considered the evidence was insufficient to allow a definitive conclusion that coadministration of erythropoietin analogues and supplemental intravenous iron was associated with an additional improvement in HRQoL.

4.2 Cost effectiveness

- 4.2.1 Five published economic analyses were available to the Committee, together with evaluations from each of the three manufacturers, and one from the Assessment Group.
- 4.2.2 Three of the five published analyses contained a cost–utility analysis. One published cost–utility analysis was performed from a UK health service perspective and considered the use of erythropoietin analogues versus the use of blood transfusions in people with stage IV breast cancer. This analysis incorporated a

- 4.2.3 The manufacturer of epoetin alfa compared the use of this treatment (with the possibility of blood transfusion) with the use of blood transfusions. A 3-year time horizon was used and the model included a survival advantage associated with erythropoietin analogues (HR = 0.64). Base-case ICERs were presented separately for different haemoglobin subgroups and for different tumour types, and were less than £16,000 per additional QALY gained.
- 4.2.4 The manufacturer of epoetin beta presented separate ICERs for solid tumours and haematological cancers, together with tumour-specific survival gains associated with erythropoietin analogues (solid tumours HR = 0.49; haematological cancers HR = 1). The associated ICERs were approximately £28,000 and £84,000 per additional QALY gained, respectively.
- 4.2.5 The manufacturer of darbepoetin alfa submitted an economic evaluation that included two scenarios. In the first, the use of darbepoetin alfa was considered over 25 weeks. The second included a time horizon of almost 3 years coupled with a treatment survival advantage (mean HR = 0.88). The associated ICERs for the two scenarios were approximately £160,000 and £24,000 per additional QALY gained, respectively.
- 4.2.6 The Assessment Group's economic evaluation used a 3-year time horizon. The model evaluated the use of erythropoietin analogues

4.2.7 In the base case of the Assessment Group's economic analysis, survival was assumed to be the same for both treatment and control arms (that is, a HR of 1 was used). This produced an ICER of more than £100,000 per additional QALY gained. The results of the sensitivity analysis demonstrated that erythropoietin analogues became more cost effective as the threshold haemoglobin concentration for initiating an erythropoietin analogue was reduced to lower levels, but the ICERs still remained high. The most favourable ICERs were obtained if a baseline haemoglobin concentration of 8 g/100 ml was assumed for all participants. These were in the range of £65,000–£80,000 per additional QALY gained.

4.2.8 The Assessment Group stated that because there was a lack of empirical data for a valid assessment of both the effect of

- 4.2.9 For the subgroup receiving platinum-based chemotherapy, when a baseline haemoglobin concentration of 8 g/100 ml was assumed and the haematological response parameters for the model were estimated from the subgroup analyses, the ICER was £39,000 per QALY.
- 4.2.10 For the subgroup receiving platinum-based chemotherapy for ovarian cancer, the lowest ICER for erythropoietin analogues was £18,000 per additional QALY gained, at an initial haemoglobin concentration of 8 g/100 ml. The Assessment Group cautioned that this result was particularly sensitive to the survival HR of 0.71 derived from the systematic review and subsequent meta-analysis. The Assessment Group noted that this survival HR estimate was based on a posthoc subgroup analysis and may have been substantially affected by trial heterogeneity. In addition, in the absence of a statistically significant difference between the subgroups with and without ovarian cancer, the Assessment Group reported that there was no evidence of a true subgroup effect in survival outcomes.
- 4.2.11 Following a reduction in the published price of erythropoietin analogues, further analyses were performed using the lowest list price of the erythropoietin analogues available for this indication (that is, £62.85 for each 10,000 IU prefilled syringe). Based on a baseline haemoglobin of 8 g/100 ml or less and assuming no effect in terms of survival (that is, HR = 1) the ICERs obtained were £30,600 and £26,200 per additional QALY for the subgroup receiving platinum-based chemotherapy for any type of cancer and

women receiving platinum-based chemotherapy for ovarian cancer, respectively.

- 4.2.12 The cost-effectiveness estimates for a treatment strategy including intravenous iron supplementation were highly sensitive to the clinical effectiveness inputs used in the analysis. Two scenarios, both using a baseline haemoglobin of 8 g/100 ml or less, were considered by applying the results of two studies that reported the outcomes needed to estimate the haematological parameters for the cost-effectiveness model. This analysis produced ICERs of £30,000 per QALY gained and in excess of £53,000 per QALY gained depending on which study was used. This analysis incorporated the lowest price following the reduction in the list price of erythropoietin analogues as above. If the assumption was included in the sensitivity analysis that 25% of people with cancer receiving blood transfusions would require an overnight stay (based on a UK study conducted between December 1996 and January 1998), the ICERs were reduced to £25,000 per additional QALY gained for the optimistic scenario. ICERs for the conservative case were still in excess of £53,000 per additional QALY gained.

4.3 *Consideration of the evidence*

- 4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of erythropoietin analogues for people with cancer treatment-induced anaemia, having considered evidence on the nature of the condition and the value placed on the benefits of erythropoietin analogues by people with the condition, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.

- 4.3.2 The Committee heard from the clinical specialists and patient experts about the consequences of fatigue resulting from anaemia induced by cancer treatment, and that fatigue related to cancer treatment was often inadequately assessed and treated. However, it understood that fatigue in people with cancer has a number of causes, and that identifying the exact contribution of anaemia following chemotherapy is very difficult in the clinical setting. The Committee heard from the clinical specialists that it was difficult to predict on the basis of haemoglobin concentration alone which people would benefit from treatment of anaemia with either blood transfusion or an erythropoietin analogue. Currently these decisions are made on a case-by-case basis, taking account of symptoms, haemoglobin concentration and patient/clinician preferences. The Committee also noted that typically only around 50% of people with cancer treatment-related anaemia experience a haematological response to erythropoietin analogue treatment.
- 4.3.3 The Committee also noted that some people preferred not to have blood transfusions and that blood transfusions could be inconvenient because of the need to attend hospital, which could require time as well as involve additional travel and other non-health related personal costs.
- 4.3.4 The Committee considered the evidence from the randomised studies and noted the effects of erythropoietin analogues on various measures of HRQoL. The Committee noted that these studies had methodological weaknesses and many of them were open-label studies. Most studies in which HRQoL was measured suggested that erythropoietin analogues improved HRQoL, but the additional benefits over standard care (that is, blood transfusions and iron supplementation if indicated) were small. The Committee was aware that standard care within the trials included blood transfusion as needed. However, the Committee was advised that

current standard care of anaemia in people with cancer is not always optimal in clinical practice, and that the need to deliver chemotherapy treatments in oncology facilities might prevent the timely delivery of blood transfusions. The Committee also noted that, in the trials, erythropoietin analogue therapy reduced the requirement for blood transfusions on average by approximately one unit per participant overall.

4.3.5 The Committee discussed the use of regular blood transfusions to achieve target haemoglobin concentrations as a possible comparator for the use of erythropoietin analogues in cancer treatment-induced anaemia. It was aware that this comparison was not part of any of the clinical trials, so it was not possible to assess the true effect of erythropoietin analogues compared with intensive blood transfusion therapy on quality of life. However, the Committee was persuaded that transfusion therapy to achieve a sustained and prolonged increase in haemoglobin concentration would be time consuming and inconvenient for most people, and trials of this type would be difficult to undertake. Moreover, such a strategy could have an impact on blood supply services and might therefore run counter to the NHS need to conserve donor blood.

4.3.6 The Committee discussed the effect of erythropoietin analogues on survival, noting the Assessment Group's finding that in none of the studies included in the assessment report's meta-analysis of survival had the technologies been used unequivocally within their current UK marketing authorisations. The Committee carefully considered the various survival estimates associated with the use of erythropoietin analogues for cancer treatment-induced anaemia that had been submitted. These included the meta-analysis of all studies included within the assessment report, the further work undertaken by the Assessment Group, and survival estimates based on meta-analyses submitted by manufacturer consultees.

4.3.7 The Committee was aware that some studies had shown improved survival benefits for erythropoietin analogues, but that other studies suggested a detrimental effect. The Committee considered various explanations for the opposing effects on survival, including the use of unlicensed doses of erythropoietin analogues, the use of erythropoietin analogues to produce haemoglobin concentrations that would now be considered too high in the light of recent safety reviews, or the use of erythropoietin analogues in people with inappropriately high starting haemoglobin levels. However, the Committee was aware that survival was not a primary endpoint in many of the studies and follow-up in these trials was of very variable duration. The Committee appreciated that there are documented biologically plausible arguments suggesting that tumour cell hypoxia may affect tumour growth and tumour response. However, the Committee understood that the relationship between haemoglobin concentration and oxygenation in tumour cells is not well established because the oxygen-carrying capacity of the blood (and, consequently, the oxygenation in the tissues) may not reflect the oxygenation in the tumour cells. Therefore, optimising oxygen-carrying capacity through anaemia treatment would not necessarily reduce hypoxia in the tumour cells.

4.3.8 The Committee also heard that there was considerable international debate about the safety of erythropoietin analogues with regard to the potential for adverse cardiovascular effects, and a biologically plausible reason to suggest possible growth-enhancing effects on some tumours, which would also support the view that erythropoietin analogues could have a negative impact on survival. The Committee therefore considered that the true effect on survival of erythropoietin analogues, when used in the management of cancer treatment-induced anaemia, remains uncertain. The Committee also noted the results of the recent safety reviews undertaken by the regulatory authorities.

Despite the additional warnings in the SPCs, the erythropoietin analogues still retain full UK marketing authorisation for this indication. On the basis of the currently available evidence the Committee concluded that no effect of erythropoietin analogues on survival could be assumed.

- 4.3.9 The Committee considered the various cost-effectiveness analyses from the manufacturers and the Assessment Group. The Committee was conscious that improvements in quality of life, however small, are highly valued by people with cancer. Nevertheless, it concluded that erythropoietin analogues were very unlikely to be cost effective if the benefits from their use for cancer treatment-induced anaemia were considered in terms of changes in quality of life alone, and it noted that the majority of the cost-effectiveness results indicated that this was the case.
- 4.3.10 The Committee noted that the economic model produced by the Assessment Group had assumed baseline haemoglobin concentrations of 13 g/100 ml or lower, and that this assumption was inconsistent with the revised UK marketing authorisations for all three drugs. The Committee considered the sensitivity analyses that had been conducted using lower baseline haemoglobin concentrations and noted that these were associated with more favourable ICERs. However, the Committee concluded that for the general case the impact of this would not result in ICERs sufficiently low to fall within a range generally considered to be cost effective.
- 4.3.11 The Committee discussed the clinical and cost effectiveness of the use of the erythropoietin analogues in conjunction with intravenous iron supplementation. The Committee noted that the UK marketing authorisations for the erythropoietin analogues indicate that everyone receiving these agents should be iron replete before

starting therapy. Thus, the additional effect of intravenous iron over and above that associated with adequate iron therapy before erythropoietin treatment was uncertain. Even so, the Committee acknowledged that it was biologically plausible that the addition of intravenous iron could enhance the effectiveness of the analogues and that in the Assessment Group's analysis, haematological response with co-administration of intravenous iron was higher than with erythropoietin analogues alone, and as a consequence the need for blood transfusion would also be reduced. The Committee noted the limitations of the available studies on the use of co-administered intravenous iron and the differences between the studies in the absolute values of the clinical outcomes reported. The Committee discussed the impact on the cost-effectiveness estimates and considered the analyses of trial data of both the most optimistic and conservative cases in which intravenous iron supplementation had been given. The Committee noted that applying the most optimistic estimates of response to erythropoietin analogues with intravenous iron supplementation produced an ICER of £30,000 per additional QALY gained, whereas taking into consideration the conservative scenario produced an ICER in excess of £53,000 per additional QALY gained. Therefore, the Committee concluded that the realistic ICER value was likely to be between these limits and thus was unlikely to fall within the range normally considered to be a cost-effective use of NHS resources. However, the Committee accepted that the additional effect of intravenous iron remained plausible and was likely to enhance the clinical and cost effectiveness of erythropoietin analogues.

- 4.3.12 The Committee also heard from the clinical specialists and patient experts that some types of cancer and cancer treatments were associated with particularly severe anaemia. There might therefore be some groups who would benefit particularly from erythropoietin

analogues, such as those with ovarian cancer or other cancers treated with platinum-based chemotherapy regimens.

4.3.13 The Committee therefore specifically considered the cost effectiveness of using erythropoietin analogues in people receiving platinum-based chemotherapy irrespective of which cancer was being treated. The Committee understood that platinum chemotherapy is known to be myelosuppressive and nephrotoxic, and was advised by the clinical specialists that platinum-based chemotherapy was therefore more commonly associated with greater degrees of anaemia. The Committee acknowledged that the effect of erythropoietin analogues in reducing the need for blood transfusion was greater in this group than in those receiving other types of cancer treatment. However, it concluded there was no sound evidence of an improvement in survival with the use of erythropoietin in this subgroup, and this would be the principal driver for cost effectiveness. The Committee also noted the reduction in the ICER for this subgroup following the reduction in the cost of erythropoietin analogues. However, despite acknowledging that it was plausible that the use of intravenous iron supplementation could improve further the response to erythropoietin analogues, the Committee concluded that this would not suffice to reduce the ICER to a range normally considered to be cost effective.

4.3.14 The Committee understood that women with ovarian cancer receiving platinum-based chemotherapy may be at risk of more profound anaemia than other people with cancer because of the particularly intense treatment schedules associated with the use of platinum therapy for ovarian cancer. The Committee next considered both cost-effectiveness estimates presented for the subgroup of people with ovarian cancer who received platinum chemotherapy. It acknowledged that these estimates referred to an

analysis in a group with a baseline haemoglobin of 8 g/100 ml or lower. The Committee noted that the principal reason for the favourable ICER in this group was the apparent survival benefit seen with erythropoietin analogues in these people. The Committee then discussed in detail the evidence base for the possible survival benefit estimate indicated in the Assessment Group's additional analysis for the group with ovarian cancer treated with platinum-based chemotherapy. The Committee was aware that this HR for survival was based on an analysis that had been derived from very few events reported in subgroups that had not been previously specified, in trials for which survival was not the primary outcome, and in which randomisation had not been stratified for known prognostic factors for survival. Moreover, the Committee was advised by the clinical specialists that to their understanding there were no reasons to expect specific survival benefits in women with ovarian cancer who received platinum-based chemotherapy. It further noted that the Assessment Group's meta-analysis suggested a greater effect of erythropoietin analogues on tumour response in people with non-ovarian cancers receiving platinum-based chemotherapy than in those with ovarian cancer. The Committee was also concerned that the Assessment Group did not have access to the subgroup data from all potentially relevant studies, and that the results for survival benefit presented may have been subject to considerable publication bias in favour of the intervention. Having considered the special characteristics associated with the use of platinum-based chemotherapy for ovarian cancer, the Committee was not persuaded by the evidence presented that a survival advantage from the use of the erythropoietin analogues had been demonstrated for this group.

- 4.3.15 However, the Committee noted that after the reduction in the list price of erythropoietin analogues was incorporated into the analysis, even if no survival benefit was assumed for the subgroup

of people with ovarian cancer receiving platinum-based chemotherapy, the ICER produced was in the region of £26,000. The Committee also recognised that this analysis applied to people with a baseline haemoglobin concentration of 8 g/100 ml or lower. The Committee concluded that, in the context of the use of the least costly product, it was appropriate to recommend the use of erythropoietin for this subgroup if used in combination with intravenous iron supplementation which would be expected to reduce the ICER still further.

4.3.16 The Committee considered the possibility that the price of blood transfusion had been underestimated in the analysis, and in particular considered the suggestion by one consultee that overnight hospital admission would be required for approximately 25% of people with cancer treatment-related anaemia receiving blood transfusion. The Committee was unconvinced by the evidence to support this point in particular, because the evidence was based on a report of practice that was more than 10 years old and was thought unlikely to be in accordance with current practice in the UK. Even so, the Committee considered the potential effect of the necessity for overnight stays on the cost-effectiveness analysis. For instance, it noted that by taking the most optimistic conclusions from the effect of intravenous iron on erythropoietin response and using the lowest currently available price of erythropoietin it was possible to calculate a theoretical ICER of £25,000 per additional QALY gained. However, the Committee concluded that this was at the lowest point of a range of plausible ICERs that extended to well over £50,000 per additional QALY gained.

4.3.17 The Committee noted the reduction in the official list price of the erythropoietin analogues that occurred during the appraisal process. The Committee acknowledged that this reduction had

substantially improved all cost-effectiveness estimates and noted that although this allowed them to recommend erythropoietin analogues for a specific subgroup, the reduction was not sufficient to change its conclusions about the cost effectiveness of erythropoietin analogues for the wider population with cancer treatment-induced anaemia or other subgroups.

- 4.3.18 The Committee then discussed the use of erythropoietin analogues in people who cannot be given blood transfusions either for clinical reasons (for example, transfusion reactions) or because of religious beliefs that include objections to blood transfusions.
- 4.3.19 With regard to religious belief, the Committee noted the Institute's report 'Social value judgements: principles for the development of NICE guidance'. This states that although respect for autonomy and individual choice are important for the NHS and its users, they should not have the consequence of promoting the use of interventions that are not clinically and/or cost effective. Within that framework, the Committee discussed whether objections based on strongly held beliefs which, for the individual concerned, have the effect of removing choice from the decision of whether to receive specific interventions should be taken into account in determining exceptions to recommendations to be applied to the wider group. It concluded that it would be appropriate to take such objections into account, and that in this case it was clear that such beliefs did have the effect of removing choice from the decision of whether to accept blood transfusion.
- 4.3.20 Considering the situations in which blood transfusion would not be possible, the Committee noted that there was little evidence on which to base an estimate of cost effectiveness in these groups, and there was no evidence to suggest that erythropoietin analogues were likely to be more cost effective in these

circumstances than in circumstances in which transfusion is available. However, the Committee was concerned that people with cancer treatment-related anaemia who could not be treated with blood transfusion could become anaemic to an extent that was likely to affect their survival. Therefore, being aware that the use of erythropoietin analogues was cost effective only if they were assumed to have an impact on survival, the Committee concluded that erythropoietin analogues could be recommended as an option for treatment as part of standard supportive care in people who are unable to receive blood transfusions and who have profound cancer treatment-related anaemia that is likely to have an impact on their survival.

- 4.3.21 The Committee discussed the issue of the scarcity of blood products and noted the 'Better blood transfusion' initiative (Health service circular 2002/009), which mandates exploring alternatives to blood transfusions. The Committee considered whether its guidance may run counter to these recommendations, but noted that the effect of treatment with erythropoietin analogues saved only one unit of blood per patient on average. Therefore, it considered that, on balance, its recommendation was sound given the currently available evidence on the clinical and cost effectiveness of erythropoietin analogues. The Committee discussed the possibility that in specific scenarios of extended scarcity of donor blood, the true cost of blood may not be fully reflected in the economic analyses. The Committee was aware that in those situations the relative cost of blood could significantly increase and then the cost effectiveness of erythropoietin analogues would be improved. However, the Committee was persuaded that this extreme situation is not foreseeable and that the full current economic cost of blood transfusion had been included in the Assessment Group's model. However, the Committee was persuaded that in the context of the use of

erythropoietin analogues as recommended in the guidance, dependence on the use of blood could be reduced in the subgroup with ovarian cancer treated with platinum chemotherapy.

4.3.22 The Committee was aware that some clinical guidelines, including those issued by the American Society for Clinical Oncology/American Society of Hematology and the European Organisation for Research and Treatment of Cancer, recommend the use of erythropoietin analogues for cancer treatment-induced anaemia in certain circumstances. However, because these guidelines were developed in a context that does not take cost effectiveness into consideration, the Committee agreed that these guidelines are not comparable to its own considerations.

4.3.23 The Committee noted that people who had already begun a course of an erythropoietin analogue for cancer treatment-induced anaemia might experience a loss of well-being if their treatment was stopped prematurely. Therefore the Committee recommended that these people who do not fall into one of the groups for which the Committee has recommended the use of erythropoietin analogues should have the option to continue their therapy until they and their specialist consider it appropriate to stop.

5 Implementation

5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals, normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.

5.2 'Healthcare standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 that requires local health boards and NHS trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.

5.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TAXXX). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Local costing template incorporating a costing report to estimate the savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives which support this locally.
- Audit support for monitoring local practice.

6 Recommendations for further research

6.1 Further research is needed to establish the effects of erythropoietin analogues in the management of anaemia induced by cancer treatment on health-related quality of life (specifically utility scores), including effects on fatigue.

- 6.2 Research is needed to confirm the benefits and risks associated with erythropoietin analogues in the management of anaemia induced by cancer treatment (specifically mortality benefits and risks). An in-depth investigation of current data is needed to identify subgroups (including those with different tumour types) in whom erythropoietin analogues may be especially cost effective.

7 Related NICE guidance

- 7.1 There is no related guidance for these technologies.

8 Date for review of guidance

- 8.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.
- 8.2 The guidance on these technologies will be considered for review in February 2009.

David Barnett
Chair, Appraisal Committee
January 2008

Appendix A. Appraisal Committee members and NICE project team

A *Appraisal Committee members*

The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice-chair. Each branch considers its own list of technologies, and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Keith Abrams

Professor of Medical Statistics, University of Leicester

Dr Jeff Aronson

Reader in Clinical Pharmacology, Department of Primary Health Care, University of Oxford

Dr Darren Ashcroft

Reader in Medicines Usage and Safety, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Professor David Barnett (Chair)

Professor of Clinical Pharmacology, University of Leicester

Dr Peter Barry

Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Professor Stirling Bryan

Head, Department of Health Economics, University of Birmingham

Professor John Cairns

Public Health and Policy, London School of Hygiene and Tropical Medicine

Dr Mark Charkravarty

Director, External Relations, Procter and Gamble Health Care, Europe

Professor Jack Dowie

Health Economist, London School of Hygiene and Tropical Medicine

Ms Lynn Field

Nurse Director, Pan Birmingham Cancer Network

Professor Christopher Fowler

Professor of Surgical Education, Barts and The London School of Medicine and Dentistry, Queen Mary, University of London

Dr Fergus Gleeson

Consultant Radiologist, Churchill Hospital, Oxford

Ms Sally Gooch

Independent Nursing and Healthcare Consultant

Mrs Barbara Greggains

Lay member

Mr Sanjay Gupta

Former Service Manager in Stroke, Gastroenterology, Diabetes and Endocrinology, Basildon and Thurrock University Hospitals Foundation NHS Trust

Mr Terence Lewis

Lay member

Professor Gary McVeigh

Professor of Cardiovascular Medicine, Queens University, Belfast; Consultant Physician, Belfast Trust

Dr Ruairidh Milne

Senior Lecturer in Public Health, National Coordinating Centre for Health Technology, University of Southampton

Dr Neil Milner

General Medical Practitioner, Tramways Medical Centre, Sheffield

Dr Rubin Minhas

General Practitioner, CHD Clinical Lead, Medway Primary Care Trust

Dr John Pounsford

Consultant Physician, Frenchay Hospital, Bristol

Dr Rosalind Ramsay

Consultant Psychiatrist, Adult Mental Health Services, Maudsley Hospital

Dr Stephen Saltissi

Consultant Cardiologist, Royal Liverpool University Hospital

Dr Lindsay Smith

General Practitioner, East Somerset Research Consortium

Mr Roderick Smith

Director of Finance, West Kent PCT

Mr Cliff Snelling

Lay member

Professor Ken Stein (Vice-Chair)

Professor of Public Health, Peninsula College of Medicine and Dentistry,
University of Exeter

Professor Andrew Stevens

Professor of Public Health, Department of Public Health and Epidemiology,
University of Birmingham

Dr Rod Taylor

Associate Professor in Health Services Research, Peninsula Medical School,
Universities of Exeter and Plymouth

B NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal) and a project manager.

Rodrigo Refoios Camejo

Technical Lead

Janet Robertson

Technical Adviser

Natalie Bemrose

Project Manager

Appendix B. Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by West Midlands Health Technology Assessment Collaboration.

- Bayliss S, Bohlius J, Brunskill S, et al. A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment, March 2005

B The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope, the assessment report and the appraisal consultation document (ACD). Organisations listed in I and II were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I Manufacturers/sponsors:

- Amgen
- Janssen-Cilag
- Roche

II Professional/specialist and patient/carer groups:

- Aplastic Anaemia Trust
- Breakthrough Breast Cancer
- British Blood Transfusion Society
- British Oncology Pharmacy Association
- British Psychosocial Oncology Society (BPOS)
- British Society for Haematology
- Cancerbackup
- International Myeloma Foundation (UK)
- Macmillan Cancer Relief
- National Blood Service
- National Cancer Alliance
- National Council for Hospice and Specialist Palliative Care
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

- Royal Pharmaceutical Society
- Tenovus The Cancer Charity
- Welsh Blood Service

III Commentator organisations (without the right of appeal):

- Association of Welsh Community Health Councils
- British National Formulary
- Institute of Cancer Research
- MRC Clinical Trials Unit
- National Cancer Research Institute
- National Collaborating Centre for Chronic Conditions
- National Public Health Service for Wales
- NHS Confederation
- NHS Purchasing and Supplies Agency
- NHS Quality Improvement Scotland

C The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on epoetin alfa, epoetin beta and darbepoetin alfa for the treatment of cancer treatment-induced anaemia by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Geoff Hall, Senior Lecturer in Medical Oncology and Honorary Consultant Physician, Cancer Research UK Clinical Centre, nominated by the Royal College of Physicians – clinical specialist
- Dr Keith MO Wilson, Senior Clinical Lecturer in Haematology, Welsh Blood Service, nominated by the Welsh Blood Service – clinical specialist
- Dr Tim J Littlewood, Consultant Haematologist, John Radcliffe Hospital, Oxford, nominated by the National Blood Service – clinical specialist

- Ms Hannah Young, nominated by Ovacome – patient expert
- Mr Lawrence Doffman, nominated by International Myeloma Foundation – patient expert