

**NATIONAL INSTITUTE FOR HEALTH AND CARE  
EXCELLENCE**

**Final appraisal determination**

**Erythropoiesis-stimulating agents (epoetin  
and darbepoetin) for treating anaemia in  
people with cancer having chemotherapy  
(including review of TA142)**

**1 Guidance**

- 1.1 Erythropoiesis-stimulating agents (epoetin alfa, beta, theta and zeta, and darbepoetin alfa) are recommended, within their marketing authorisations, as options for treating anaemia in people with cancer who are having chemotherapy.
- 1.2 If different erythropoiesis-stimulating agents are equally suitable, the product with the lowest acquisition cost for the course of treatment should be used.

**2 Clinical need and practice**

- 2.1 Anaemia is defined as a haemoglobin concentration, red cell count, or packed cell volume below normal levels. The World Health Organization defines anaemia as a haemoglobin concentration of less than 120 g/litre in women and less than 130 g/litre in men. Erythropoiesis, the production of red blood cells, occurs in the bone marrow, needs iron and is stimulated by the hormone erythropoietin, which is produced in the kidneys. Cancer treatment can suppress the production of red blood cells in the bone marrow. Once cytotoxic chemotherapy stops, haemoglobin can return to pre-treatment concentrations.

- 2.2 Anaemia can compromise the effect of treatment for cancer, reduce survival, and cause symptoms that affect quality of life. Mild-to-moderate anaemia can cause headache, palpitations, tachycardia and shortness of breath. Chronic anaemia can damage organs. Severe fatigue is the most common symptom, and can lead to an inability to perform everyday tasks.
- 2.3 Approximately 60% of people with solid tumours who have chemotherapy develop anaemia, with a haemoglobin concentration of less than 110 g/litre. The incidence of anaemia is highest in people with lung cancer (71%) and gynaecological cancer (65%) because these cancers currently involve treatment with platinum-based chemotherapy. The proportion of people with solid tumours who need a red blood cell transfusion because of their anaemia varies from 47% to 100% depending on the stage of the cancer, the cumulative dose of platinum chemotherapy, the person's age and pre-treatment haemoglobin concentration. For haematological cancers, about 70% of people with lymphoma have anaemia after 3 to 4 cycles of chemotherapy.
- 2.4 Anaemia associated with cancer treatment is managed by adjusting the cancer treatment regimen, giving iron supplements and, if anaemia is severe, transfusing red blood cells. Problems related to blood transfusions may potentially include a limited supply of blood, iron overload, immune injury, and viral and bacterial infections. [Epoetin alfa, epoetin beta and darbepoetin alfa for cancer treatment-induced anaemia](#) (NICE technology appraisal guidance 142) recommends erythropoietin analogues plus intravenous iron as an option for managing cancer treatment-induced anaemia in women having platinum-based chemotherapy for ovarian cancer and who have symptoms associated with anaemia and a haemoglobin concentration of 80 g/litre or lower. Clinicians may also consider erythropoietin analogues for people who cannot have

blood transfusions and who have profound cancer treatment-related anaemia that is likely to affect survival.

### **3 The technologies**

3.1 Epoetin and darbepoetin are erythropoiesis-stimulating agents.

#### ***Epoetins***

3.2 Epoetin alfa, beta, theta and zeta are recombinant human erythropoietin analogues used to shorten the period of symptomatic anaemia in people having cytotoxic chemotherapy. Epoetins are recommended for use when haemoglobin concentrations are 100 g/litre or lower, and target values up to 120 g/litre.

#### **Epoetin alfa**

3.3 There are 2 brands of epoetin alfa (Eprex, Janssen-Cilag and Binocrit, Sandoz), and both have UK marketing authorisations for the 'treatment of anaemia and reduction of transfusion requirements in adult patients receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma, who are at risk of transfusion as assessed by the patient's general status (for example, cardiovascular status, pre-existing anaemia at the start of chemotherapy)'. Binocrit is a biosimilar medicine referenced to Eprex (see section 3.18).

3.4 The summary of product characteristics for Eprex and Binocrit lists headache, nausea and pyrexia as very common adverse reactions, and deep vein thrombosis, hypertension, pulmonary embolism, diarrhoea, vomiting, rash, arthralgia and influenza-like illness as common adverse reactions in patients with cancer. The summary of product characteristics for Binocrit also lists stroke as a common adverse reaction. For full details of adverse reactions and contraindications, see the summary of product characteristics.

- 3.5 Eprex and Binocrit are available in pre-filled syringes at net prices of £5.53 and £4.33 per 1000 units respectively (excluding VAT; British national formulary [BNF], March 2014). They are administered by subcutaneous injection at a recommended initial dose of 150 units/kg body weight 3 times weekly or 450 units/kg body weight once a week. Costs may vary in different settings because of negotiated procurement discounts.

### **Epoetin beta**

- 3.6 Epoetin beta (NeoRecormon, Roche Products) has a UK marketing authorisation for the 'treatment of symptomatic anaemia in adult patients with non-myeloid malignancies who are receiving chemotherapy'.
- 3.7 The summary of product characteristics lists the following common adverse reactions for epoetin beta in patients with cancer: hypertension, thromboembolic event and headache. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 3.8 Epoetin beta is available in a pre-filled syringe at a net price of £3.51 per 500 units (excluding VAT; BNF, March 2014). It is administered by subcutaneous injection at a recommended initial dose of 450 units/kg body weight once a week or in divided doses 3 to 7 times a week. Costs may vary in different settings because of negotiated procurement discounts.

### **Epoetin theta**

- 3.9 Epoetin theta (Eporatio, Teva UK) has a UK marketing authorisation for the 'treatment of symptomatic anaemia in adult patients with non-myeloid malignancies who are receiving chemotherapy'.

- 3.10 The summary of product characteristics lists the following common adverse reactions for epoetin theta in patients with cancer: headache, hypertension, skin reactions, arthralgia and influenza-like illness. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 3.11 Epoetin theta is available in a pre-filled syringe at a net price of £5.99 per 1000 units (excluding VAT; BNF, March 2014). It is administered by subcutaneous injection at a recommended initial dose of 20,000 units once a week. Costs may vary in different settings because of negotiated procurement discounts.

### **Epoetin zeta**

- 3.12 Epoetin zeta (Retacrit, Hospira UK) is a biosimilar medicine referenced to Eprex (see section 3.18). It has a UK marketing authorisation for the ‘treatment of anaemia and reduction of transfusion requirements in adult patients receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma, who are at risk of transfusion as assessed by the patient’s general status (for example, cardiovascular status, pre-existing anaemia at the start of chemotherapy)’.
- 3.13 The summary of product characteristics for epoetin zeta lists headache as a very common adverse reaction, and stroke, dizziness, deep vein thrombosis, an increase in blood pressure, pulmonary embolism, non-specific skin rashes, joint pains, flu-like symptoms, feeling of weakness, and tiredness as common adverse reactions in patients with cancer. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 3.14 Epoetin zeta is available in a pre-filled syringe at a net price of £5.66 per 1000 units (excluding VAT; BNF, March 2014). It is administered by subcutaneous injection at a recommended initial

dose of 150 units/kg body weight 3 times weekly or 450 units/kg body weight once a week. Costs may vary in different settings because of negotiated procurement discounts.

### ***Darbepoetin alfa***

- 3.15 Darbepoetin alfa (Aranesp, Amgen) is a hyperglycosylated derivative of epoetin that stimulates erythropoiesis by the same mechanism as the endogenous hormone. Aranesp has a UK marketing authorisation for the 'treatment of symptomatic anaemia in adult cancer patients with non-myeloid malignancies who are receiving chemotherapy'. The summary of product characteristics recommends that darbepoetin alfa should be used at haemoglobin concentrations of 100 g/litre or lower, with target values up to 120 g/litre.
- 3.16 The summary of product characteristics for darbepoetin alfa lists hypersensitivity and oedema as very common adverse reactions, and hypertension, thromboembolic events (including pulmonary embolism), rash/erythema and injection-site pain as common adverse reactions in patients with cancer. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 3.17 Darbepoetin alfa is available in a pre-filled syringe at a net price of £14.68 per 10 micrograms (excluding VAT; BNF, March 2014). It is administered by subcutaneous injection at a recommended initial dose of 500 micrograms (6.75 micrograms/kg body weight) once every 3 weeks or 2.25 micrograms/kg body weight once a week. Costs may vary in different settings because of negotiated procurement discounts.

## ***Biosimilars***

- 3.18 This appraisal includes 2 biosimilar medicines, Binocrit and Retacrit, both of which are referenced to Eprex. The British National Formulary (May 2014) states: 'A biosimilar medicine is a new biological product that is similar to a medicine that has already been authorised to be marketed (the biological reference medicine) in the European Union. The active substance of a biosimilar medicine is similar, but not identical, to the biological reference medicine. Biological products are different from standard chemical products in terms of their complexity and although theoretically there should be no important differences between the biosimilar and the biological reference medicine in terms of safety or efficacy, when prescribing biological products, it is good practice to use the brand name. This will ensure that substitution of a biosimilar medicine does not occur when the medicine is dispensed'.

## **4 Evidence and interpretation**

The Appraisal Committee (section 8) considered evidence from several sources (section 9).

### **4.1 *Clinical effectiveness***

- 4.1.1 The Assessment Group identified 23 randomised controlled trials (RCTs) evaluating the effectiveness and safety of erythropoiesis-stimulating agents (ESAs) for treating cancer treatment-related anaemia. These included 16 trials from the previous review by Wilson et al. (2007) used in [Epoetin alfa, epoetin beta and darbepoetin alfa for cancer treatment-induced anaemia](#) (NICE technology appraisal guidance 142). The Assessment Group stated that none of the identified trials evaluated ESAs entirely in line with their marketing authorisations, which had been modified because of safety concerns when treating haemoglobin concentrations over 100 g/litre. Therefore, the Assessment Group's review focused only

on trials that evaluated ESAs at a starting dose reflecting the current licence, whether or not the studies treated patients at concentrations of haemoglobin in line with that of the current licences.

- 4.1.2 Of the 23 included trials, 13 compared ESAs plus standard care with placebo plus standard care. The remaining 10 studies were not placebo-controlled and compared ESAs plus standard care with standard care alone. The Assessment Group did not address the relative effectiveness of different ESAs because it found only 1 trial that compared 1 ESA with another. The Assessment Group stated that some trials omitted important information and that all the trials were flawed in some way; in particular, it noted that no trial clearly reported methods of how patients were allocated to treatments.
- 4.1.3 In most of the trials, erythropoietin therapy was given to patients throughout the course of chemotherapy and, in some trials, continued for 4 weeks after chemotherapy. The average duration of treatment with erythropoietin was 12 weeks. Some of the trials allowed concomitant treatments for anaemia including granulocyte colony-stimulating factor, iron and red blood cell transfusions. Sixteen trials provided intravenous or oral iron to patients.
- 4.1.4 The age of patients in the trials ranged from 18 years to 92 years. There was an equal distribution of men and women in trials other than those of gynaecological and breast malignancies. The trials included patients with various types of malignancies (for example, solid, haematological or mixed). Cancer treatments used in the trials consisted of platinum-based chemotherapy (4 trials), non-platinum-based chemotherapy (6 trials), mixed chemotherapy, that is, platinum- and non-platinum-based chemotherapy (6 trials), and chemotherapy plus radiotherapy (1 trial). In 6 studies, the publications did not report the type of chemotherapy used.

4.1.5 The Assessment Group grouped the outcomes from the included studies into 4 categories:

- outcomes related to anaemia including:
  - mean change in haemoglobin concentration from the start to the end of the treatment period
  - haematological response (defined as the proportion of patients whose haemoglobin concentration increased by 20 g/litre or more, or whose haematocrit increased by 6% or more)
  - red blood cell transfusion needs (including the proportion of patients who had transfusions, number of units transfused per patient and average number of units transfused per patient)
- outcomes related to cancer (complete tumour response, overall survival and on-study mortality)
- adverse events
- health-related quality of life.

4.1.6 The Assessment Group pooled the results of the individual trials using a random-effects model. It considered patients randomised to any erythropoietin analogue, together classed as the 'ESA group', whereas the group of patients treated without an ESA included patients randomised to placebo plus standard care, or standard care alone. The Assessment Group conducted sensitivity analyses for each outcome using fixed-effects meta-analyses, and compared these with the results of the Cochrane review by Tonia et al. (2012) and of the review by Wilson et al. (2007). Where data were available, the Assessment Group conducted subgroup analyses using:

- the concentration of haemoglobin at which patients had their anaemia treated
- the haemoglobin concentration after treatment

- the type of malignancy (and specifically whether or not a patient had ovarian cancer)
- the type of cancer treatment
- whether short-lasting epoetin or long-lasting darbepoetin was used
- whether or not the patient received iron
- the duration of ESA treatment
- whether the trials were placebo-controlled or not.

The Assessment Group indicated that few of the subgroup analyses had sufficient power to identify true differences.

### **Outcomes related to anaemia**

4.1.7 The Assessment Group's random-effects analysis of mean haemoglobin change included 16 trials (n=3170) and showed a statistically significant weighted mean difference (WMD) between patients treated with an ESA and patients treated without an ESA of 15.9 g/litre from the start to the end of treatment (95% confidence interval [CI] 1.33 to 1.84). There was considerable heterogeneity between the trials ( $I^2=75.9%$ ,  $p<0.001$ ), although in all trials ESAs increased haemoglobin concentration. The fixed-effects analysis also showed a statistically significant difference in haemoglobin change in favour of the ESA group, and also showed considerable heterogeneity (WMD 14.9 g/litre, 95% CI 1.37 to 1.60,  $I^2=75.9%$ ,  $p<0.001$ ). Although ESAs increased haemoglobin concentration across all subgroups, there were statistically significant ( $p<0.05$ ) differences between the types of ESA and between chemotherapy treatments. The analysis showed that epoetin treatment offered greater benefits than darbepoetin treatment, and that the ESAs were more effective in the trials with mixed chemotherapy than in the trials with platinum-based chemotherapy only, trials with non-platinum-based chemotherapy only or trials in which the cancer treatment was not reported. The

Assessment Group emphasised that the subgroup results were uncertain because of the small number of studies, and because it had not adjusted the subgroup analyses for multiple testing.

- 4.1.8 Using a random-effects model and the results of a meta-analysis of 10 trials (n=2228), the Assessment Group reported a statistically significant difference in haematological response in favour of ESA treatment compared with treatment without an ESA (risk ratio [RR] 3.29, 95% CI 2.84 to 3.81). Using a fixed-effects model, the risk ratio was 3.41 (95% CI 2.96 to 3.92). All the individual trials showed a beneficial effect of ESA treatment with little heterogeneity ( $I^2=6.4%$ ,  $p=0.383$ ).
- 4.1.9 Fewer patients randomised to ESA treatment than patients randomised to treatment without an ESA (554 of 2480 compared with 835 of 2299 patients respectively) needed blood transfusions in the 22 trials that assessed transfusion needs. The risk ratio was 0.63 (95% CI 0.57 to 0.69) for the random-effects analysis and 0.62 (95% CI 0.51 to 0.67) for the fixed-effects analysis, indicating a statistically significant difference between treatment arms. The Assessment Group found little heterogeneity ( $I^2=10.5%$ ,  $p=0.315$ ), and all but 1 study showed a beneficial effect of ESA treatment.
- 4.1.10 In addition to evaluating whether patients needed blood transfusions, the Assessment Group evaluated whether there was a difference in how many units of blood a patient having transfusions needed. The Assessment Group reported that, based on 10 studies evaluating 1920 patients, patients randomised to an ESA compared with patients not randomised to an ESA needed fewer units of blood transfused (WMD  $-0.87$ , 95% CI  $-1.28$  to  $-0.46$  using the random-effects model; and WMD  $-0.64$ , 95% CI  $-0.79$  to  $-0.48$  using the fixed-effects model). The Assessment Group found moderate heterogeneity between trials ( $I^2=59.3%$ ,  $p=0.006$ ), and all but 1 study showed that patients treated with an

ESA needed fewer units of blood transfused than did patients treated without an ESA. The effect of ESA treatment in reducing the number of units of blood transfused was consistent across all subgroups, except for the subgroup characterised by having taken part in studies with treatment lengths of 17–20 weeks (WMD 0.10, 95% CI –0.59 to 0.79).

### **Outcomes related to cancer**

4.1.11 Whether or not a patient's cancer responded to treatment was measured as 'complete tumour response' in 7 studies comprising 1909 patients. Randomisation to ESA treatment was associated with a pooled risk ratio of 1.10 (95% CI 0.86 to 1.41) for complete tumour response compared with randomisation to treatment without an ESA. The Assessment Group did not find significant heterogeneity between the trials; however, the direction of effect did vary between trials. The fixed-effects analysis showed similar results of no difference between patients treated with and without an ESA (RR 1.20, 95% CI 0.85 to 1.71). The Assessment Group highlighted that the review by Wilson et al. (2007) showed that randomisation to ESAs compared with randomisation to treatment without an ESA worsened tumour response (RR 1.31, 95% CI 1.08 to 1.60), whereas the review by Tonia et al. (2012) did not find any difference (RR 1.02, 95% CI 0.98 to 1.06).

4.1.12 To assess whether ESAs prolonged or shortened overall survival, the Assessment Group extracted summary data from the Cochrane review by Tonia et al. (2012), which had used individual patient data. The Assessment Group's meta-analysis included 18 trials comprising 4454 patients, in which 818 out of 2317 patients in the ESA group and 744 out of 2137 patients treated without an ESA had died. The pooled hazard ratio for the association of treatment with an ESA and death was 0.97 (95% CI 0.83 to 1.13), showing no difference in survival; there was moderate heterogeneity between

the trials ( $I^2=42.4\%$ ,  $p=0.03$ ). The fixed-effects analysis showed a similar result (hazard ratio [HR] 0.98, 95% CI 0.89 to 1.08) as did the review by Wilson et al. (2007) (HR 1.03, 95% CI 0.92 to 1.16). This differed from the findings of the Cochrane review by Tonia et al., which reported that ESAs increased the risk of death (HR 1.05, 95% CI 1.00 to 1.11). The Assessment Group emphasised that its analysis included only studies complying with the licensed ESA starting dose, whereas the Cochrane review did not restrict trials based on dose.

- 4.1.13 The Assessment Group's meta-analysis of mortality during the study period included 14 studies comprising 2967 patients. The Assessment Group reported no difference in the risk of death (HR 0.86, 95% CI 0.67 to 1.11) and no heterogeneity between the trials ( $I^2=16.4\%$ ,  $p=0.274$ ). The fixed-effects analysis also showed no difference in the risk of death (HR 0.87, 95% CI 0.70 to 1.09), whereas the Cochrane review by Tonia et al. (2012) showed that ESA treatment increased the risk of death (HR 1.17, 95% CI 1.03 to 1.29).

### **Adverse events**

- 4.1.14 The Assessment Group conducted meta-analyses (using data from the Cochrane review by Tonia et al. 2012) to address whether, and to what degree, ESA treatment was associated with the following adverse events: thromboembolic events (14 trials,  $n=4013$ ); hypertension (9 trials,  $n=2032$ ); thrombocytopenia and haemorrhage (7 trials,  $n=1715$ ); seizures (1 trial,  $n=289$ ); and pruritus (pruritus, rash and irritation; 6 trials,  $n=869$ ). The random-effects analysis showed that ESA treatment increased the risk of thromboembolic events (RR 1.46, 95% CI 1.07 to 1.99), hypertension (RR 1.80, 95% CI 1.14 to 2.85) and pruritus (RR 2.04, 95% CI 1.11 to 3.75) compared with treatment without an ESA. ESA treatment was not associated with seizures (RR 1.19, 95% CI

0.33 to 4.38), or thrombocytopenia and haemorrhage (RR 0.93, 95% CI 0.65 to 1.34). The Assessment Group reported similar results for the fixed-effects analyses.

## Subgroups

- 4.1.15 The Assessment Group presented subgroup analyses exploring key elements of the recommendations in [NICE technology appraisal guidance 142](#). It presented results for subgroups according to chemotherapy, cancer type and other anaemia treatments as follows: patients with any cancer having platinum-based chemotherapy (5 trials, n=1119); patients with ovarian cancer having platinum-based chemotherapy (1 trial, n=122); patients having iron supplementation (16 trials); and patients unable to have blood transfusions. The Assessment Group noted that the results were uncertain given the small number of studies supplying data for each subgroup, and it had not adjusted the results for multiple testing. However, it noted that, in patients having platinum-based chemotherapy, the response was generally better than in patients who received other chemotherapy. The Assessment Group did not identify any trials that evaluated the use of ESAs in patients unable or unwilling to have blood transfusions. It commented that it had trouble interpreting the results of the trials that used ESAs with iron because there are many types of iron supplements, and because few publications reported these results.
- 4.1.16 The Assessment Group conducted an analysis of patients with a haemoglobin concentration of 110 g/litre or less at the start of treatment (14 trials) and with target haemoglobin values of 130 g/litre or less (2 trials); the Assessment Group considered that these patients more closely reflected the marketing authorisations for ESAs. For anaemia-related outcomes, when using this subset of trials, the Assessment Group found estimates of the effectiveness of ESAs similar to those from meta-analyses from all of the trials

included in the review. The analysis showed that ESAs do not increase or decrease the risk of death (inclusion concentration of 110 g/litre or less; HR 0.91, 95% CI 0.70 to 1.20). The analysis also showed that the risks of thromboembolic events (RR 1.29, 95% CI 0.66 to 2.54) and hypertension (RR 1.68, 95% CI 1.03 to 2.74) were slightly lower in this subgroup than in the overall population. When assessing the 2 trials in which investigators also limited the target haemoglobin concentration to 130 g/litre or less, ESA treatment did not increase or decrease the risk of death (HR 0.50, 95% CI 0.20 to 1.23).

### **Health-related quality of life**

4.1.17 In its review of health-related quality of life, the Assessment Group included 13 randomised controlled trials that measured quality of life. The Assessment Group reported that treatment with an ESA compared with treatment without an ESA improved quality of life more, and reported a difference in scores of Functional Assessment of Cancer Therapy-Fatigue (FACT-F) (WMD 2.54, 95% CI 1.42 to 3.65), with low heterogeneity between the trials ( $I^2=14.9%$ ,  $p=0.32$ ). The Assessment Group reported similar results for its fixed-effects analysis. The Assessment Group stated that a clinically important difference in quality of life is considered to be a value of greater than 3.0 (Cella et al. 2002). For the FACT-General (G) and FACT-Anaemia (An) outcomes, the Assessment Group included 3 studies that showed no difference between the treatment arms (FACT-G: WMD 2.98, 95% CI -0.83 to 6.78; FACT-An: WMD 2.60, 95% CI -0.52 to 5.72). However, the Assessment Group noted that the quality-of-life data were limited by substantial missing data.

## **4.2 Cost effectiveness**

4.2.1 The Assessment Group identified 10 existing cost-utility studies. It noted that starting doses of the ESAs used by the authors in the

cost–utility studies generally reflected the licensed doses, although the concentrations of haemoglobin at which a clinician would start and stop treatment were not reported. The Assessment Group stated that some of the studies estimated quality of life as a function of haemoglobin concentrations.

4.2.2 The analyses by Wilson et al. (2007) and Martin et al. (2003) were performed from a UK health service perspective and estimated incremental cost-effectiveness ratios (ICERs) of £150,000 and £8851 per quality-adjusted life year (QALY) gained respectively. The study by Martin et al. was based on patients with metastatic breast cancer, and assumed that ESA treatment increases survival. The Assessment Group stated that this subgroup was identified post hoc from a trial that was not powered to detect survival differences.

4.2.3 None of the manufacturers of the ESAs included in the appraisal submitted an economic evaluation for this appraisal.

#### **Assessment Group's cost-effectiveness analysis**

4.2.4 The Assessment Group developed a simple empirical model to assess the cost effectiveness of ESA treatment. The model had 2 arms (treatment with or without an ESA) and 2 components: a short-term component (during treatment and during the time over which the haemoglobin returns to normal concentrations) and a long-term component. The Assessment Group modelled short-term QALYs as changes in haemoglobin concentrations over time seen in the clinical trials, and long-term QALYs by estimating overall survival in each arm and applying a long-term utility common to both arms. The Assessment Group based the analyses on a lifetime time horizon from an NHS and personal social services perspective. Costs and benefits were discounted at an annual rate of 3.5%. The mean age of modelled patients was 59.1 years and

the mean weight was 66.6 kg, which was taken from the Assessment Group's systematic review of clinical effectiveness.

- 4.2.5 To estimate the magnitude of effectiveness of ESAs, the Assessment Group used trials reporting intention-to-treat analyses. The Assessment Group took parameters, including difference in haemoglobin change from baseline, difference in number of red blood cell units transfused, overall survival hazard ratio, relative risk and probability of adverse events (thromboembolic events, hypertension and thrombocytopenia), directly from its random-effects meta-analyses. For other parameters such as change in haemoglobin from baseline in patients treated without an ESA and mean number of red blood cell units transfused in patients treated without an ESA, the Assessment Group calculated the weighted averages from the control arms of the studies included in its meta-analyses. The Assessment Group estimated patients' baseline haemoglobin concentration as 103.8 g/litre based on the weighted average of the studies included in its review. In its base case, the Assessment Group assumed that all ESAs are equally effective.
- 4.2.6 The Assessment Group assumed a 'normalisation period' in the model, when patients' haemoglobin concentrations increase at a constant rate until they reach normal concentrations. Based on the opinions of clinical specialists, the Assessment Group assumed the same rate (2 g/litre per week) for both treatment arms, that is, patients treated with or without an ESA during chemotherapy. This value was consistent with previous cost–utility studies.
- 4.2.7 To extrapolate overall survival in patients treated with or without ESAs, the Assessment Group first modelled survival in the control arm by taking a weighted geometric average of the overall survival rate seen in the control arms of all the included trials. It chose an exponential distribution. It then derived a hazard ratio from its meta-analysis, and used this to estimate survival in the ESA arm. The

Assessment Group estimated a mean overall survival of 2.76 years for patients treated with an ESA and 2.67 years for patients treated without an ESA. In its base case, the Assessment Group assumed that patients treated with ESAs died later than those not treated with ESAs, and used a hazard ratio of 0.97 in its base case. It also explored alternative scenarios, notably that treatment with ESAs does not prolong survival (HR=1.0).

- 4.2.8 To estimate the utility contributing to the short-term QALY gains in the model, the Assessment Group did not use the FACT-F scores measured in some of the trials. Instead, it modelled utility as a function of haemoglobin concentration. It used utility values from the literature, specifically from a study by Harrow et al. (2011) in which SF-36 utility values were measured in 13,433 women in the USA with cancer and valued by the UK general public using the standard gamble technique to transform them to SF-6D values. The Assessment Group highlighted that the patient population in the study included only patients who were not treated with ESAs and who may or may not have been having chemotherapy. The Assessment Group then expressed the SF-6D values as EQ-5D values using regression analyses from Brazier et al. (2004). The SF-6D utility increase of 0.009 per unit increase in haemoglobin concentrations translated to an EQ-5D utility increase of 0.028 per increase of 10 g/litre in haemoglobin concentration. The Assessment Group applied an increase in utility of 0.028 per each 10 g/litre rise in haemoglobin until a patient's haemoglobin concentration reached 120 g/litre. The Assessment Group adjusted for mean difference in haemoglobin concentrations between the treatment arms in the model.
- 4.2.9 To estimate utility in the long-term component of the model, that is, after a patient's haemoglobin had reached 120 g/litre, the Assessment Group applied age-related utility calculations from Ara

and Brazier (2010) to the utilities reported by Tengs and Wallace (2000), resulting in a constant utility value of 0.76 for both treatment arms. The Assessment Group stated that, because of sparse data, the estimated utility was uncertain and could affect the overall QALYs accrued. The Assessment Group did not include disutilities associated with adverse reactions when calculating QALYs because it considered that the trials did not clearly report adverse events. However, the Assessment Group stated that including disutilities associated with adverse reactions would increase the ICERs because patients treated with ESAs experienced more adverse reactions than patients not treated with ESAs (see section 4.1.14).

- 4.2.10 To cost the ESAs, the Assessment Group used the list price per 1000 units from the British national formulary (BNF, March 2014) for Eprex (£5.53), Binocrit (£5.09), NeoRecormon (£7.01), Eporatio (£5.99) and Retacrit (£5.66), and per microgram for Aranesp (£1.47). To calculate a mean weekly dose, the Assessment Group combined into a single parameter the rates of withdrawing from ESA treatment, increasing the dose, and decreasing the dose reductions estimated from the trials included in its review of clinical effectiveness. The Assessment Group used an average body weight of 66.6 kg to convert from weight-based doses to fixed doses. The Assessment Group estimated a fixed dose of 24,729 units per week for Eprex, Binocrit and Retacrit, and fixed doses of 31,021 units for NeoRecormon, 22,859 units for Eporatio and 141.1 micrograms for Aranesp. The Assessment Group assumed that the duration of ESA treatment was 12 weeks based on its review of clinical effectiveness.
- 4.2.11 Based on the opinions of clinical specialists, the average cost per administration of an ESA used in the model was £8.16. This was estimated from the personal social services research unit (PSSRU)

and weighted by the probability of being administered by a district nurse (21.6%), a GP nurse (21.6%) or a hospital staff nurse (16.3%), or being self-administered (40.6%). In its base-case analysis, the Assessment Group assumed that patients would have ESAs once a week (based on the marketing authorisations and the included trials) for 12 weeks. The Assessment Group did not model ESA treatment after a patient achieved haemoglobin of 120 g/litre, although it noted that in clinical practice some patients continue ESA treatment up to 4 weeks after chemotherapy.

- 4.2.12 The unit cost for the supply of red blood cell was taken from NHS Blood and Transplant and inflated to 2014/15 prices. In the absence of more recent data, the Assessment Group derived the cost of an appointment for a transfusion from the study by Varney and Guest (2003). The Assessment Group assumed that patients who do or do not have treatment with ESAs are equally likely to need iron supplements; therefore, it did not include the cost of iron supplements in the analysis.
- 4.2.13 The Assessment Group assumed that a patient would have blood tests regularly during chemotherapy, whether or not they were treated for anaemia, and that patients treated with an ESA would have 4 additional blood tests post-chemotherapy. The Assessment Group estimated the cost for the additional blood tests from PSSRU and NHS reference costs. The Assessment Group obtained costs of treating adverse reactions (thromboembolic events, hypertension and thrombocytopenia) by pooling the results of studies included in its review, and from NHS reference costs. The Assessment Group assumed that patients in the model would experience, at most, 1 adverse reaction of each type. It assumed that the dosing schedule, administration cost, cost of red blood cell transfusion, additional blood tests and adverse reactions were similar for all the ESAs.

- 4.2.14 The base-case analysis that used parameters from all studies resulted in ICERs ranging from £19,429 per QALY gained for Binocrit to £35,018 per QALY gained for NeoRecormon compared with no ESA treatment. The incremental costs of the ESAs compared with no ESA treatment ranged from £1371 for Binocrit to £2472 for NeoRecormon, whereas the incremental QALY gain was 0.0706 for all ESAs compared with no ESA treatment.
- 4.2.15 The Assessment Group noted that more than three-quarters of the total QALY gain associated with ESA use (0.0706) were accrued in the long-term component of the model (0.0582). The Assessment Group found that the estimated short-term QALY gain of 0.0124 was lower than those reported in other analyses of cost effectiveness, such as in the review by Wilson et al. (2007), which reported a short-term QALY gain of 0.030.
- 4.2.16 In the Assessment Group's probabilistic analysis, the ICERs ranged from £14,724 per QALY gained for Binocrit to £27,226 per QALY gained for NeoRecormon. The 95% credible intervals covered a range of £2322 per QALY gained to dominated (that is, the ESAs had higher costs and lower QALYs than treatments not including ESAs). At a maximum acceptable ICER of £20,000 per QALY gained, Binocrit had less than 25% chance of being cost effective, whereas the other ESAs had less than 20% chance of being cost effective.

### **Scenario analyses**

- 4.2.17 The Assessment Group explored a scenario in which patients using ESAs do not live longer than patients not using ESAs. This resulted in a long-term QALY gain of 0 and an overall QALY gain of 0.0124 (reflecting the short-term QALY gain only). This analysis resulted in an ICER of more than £110,000 per QALY gained for patients using ESAs compared with patients not using ESAs. The

probabilistic sensitivity analysis resulted in ICERs ranging from £96,754 per QALY gained for Binocrit to £174,193 per QALY gained for NeoRecormon.

- 4.2.18 In a second scenario analysis, the Assessment Group applied the best contract prices available for the ESAs to its base-case analysis, rather than using BNF prices. The contract prices reflect the actual prices paid by the NHS for ESAs based on a 'price-volume' agreement with the manufacturers. The contract prices used in this scenario represented the latest tenders to London hospitals provided to NICE for this appraisal by the Commercial Medicines Unit and the South East England Specialist Pharmacy Services, with the manufacturers' consent. These prices are designated as commercial in confidence. The ICERs are also commercial in confidence because they allow the contract prices to be calculated. Using these prices, the ICERs were considerably lower. Retacrit generated the lowest ICER and Aranesp the highest ICER; however, the Assessment Group stated that the probabilistic analysis of incremental net health benefits suggests that the cost effectiveness of the ESAs were similar.
- 4.2.19 When the Assessment Group combined these 2 scenario analyses, applying contract prices and assuming that people using ESAs do not live any longer than people not using ESAs, the ICERs were lower than the base-case estimates (these ICERs are designated commercial in confidence). The probability that the ESA with the lowest contract price would be cost effective at a threshold of £20,000 per QALY gained was above 50%. The Assessment Group noted that the most important drivers of the cost-effectiveness results included the price at which the NHS buys ESAs, and the assumption that ESAs prolong survival.
- 4.2.20 In another scenario, using the base-case drug prices and assuming that ESA treatment improves survival (as estimated from the base

case) but for the first 3 years only (after which the death rate is equal for both treatment arms), the Assessment Group estimated an ICER range of £42,584 per QALY gained for Binocrit to £76,751 per QALY gained for NeoRecormon. The Assessment Group highlighted that the results suggest that 66% of the long-term QALY gain and 54% of the total QALY gain in the base case accrues over the first 3 years after ESA treatment.

- 4.2.21 To estimate ICERs more closely reflecting the marketing authorisation, the Assessment Group performed a scenario analysis using only trials in which the haemoglobin concentration of patients was 110 g/litre or less when starting treatment. The baseline haemoglobin concentration estimated using this subgroup of trials was 94 g/litres compared with 103.8 g/litres estimated in the base case. The Assessment Group used most cost and utility input parameters from the base case. The resulting deterministic ICERs ranged from £12,593 per QALY gained for Binocrit to £23,013 per QALY gained for NeoRecormon. The probabilistic analysis resulted in ICERs ranging from £10,363 to £19,157 per QALY gained, with the upper limit of the 95% credible intervals indicating that treatment without ESAs dominated treatment with any ESA.

### **Univariate sensitivity analyses**

- 4.2.22 The Assessment Group performed various univariate (one-way) sensitivity analyses around the base-case ICERs. To assess the effect of the utility associated with increasing haemoglobin concentrations on the ICERs, the Assessment Group assumed alternate values of 0.009 (SF-6D value from Harrow et al. 2011) and 0.016 (EQ-5D value from Tajima et al. 2010) for anaemia related to chronic kidney disease. Using the values of 0.016 and 0.009 slightly increased the base-case ICERs. However, applying a higher utility value of 0.06 (Wilson et al. 2007) decreased the base-

case ICERs to below £30,000 per QALY gained for NeoRecormon and Aranesp, and to below £20,000 per QALY gained for all the other ESAs compared with treatment without an ESA. When the Assessment Group included in the model long-term costs of £20,000 per year associated with ongoing cancer treatment (such as costs of maintenance therapy, subsequent chemotherapy cycles or relapse), the ICERs of all the ESAs increased to levels above £30,000 per QALY gained. Applying alternative dosing schedules within the marketing authorisations of the ESAs (see section 3) generally increased the ICERs slightly. All other scenarios had little effect on the base-case ICERs, including using the ESA administration schedule for chronic kidney disease-related anaemia (that is, nurse administration [25%] and self-administration [75%]), and using higher and lower values for the cost of a blood transfusion appointment and the cost of treating adverse reactions.

4.2.23 The Assessment Group highlighted the large difference between the lowest base-case ICER reported in the current review (£19,429 per QALY gained) and the base-case ICER reported in [NICE technology appraisal guidance 142](#) by Wilson et al. (2007) (£150,342 per QALY gained). In exploring these differences, the Assessment Group adjusted its model to incorporate some parameters used in NICE technology appraisal guidance 142. The adjustments increased the base-case ICER for the most cost-effective ESA from £19,429 to £109,055 per QALY gained. The Assessment Group noted that the parameters from the current appraisal that affected the results were:

- lower short-term QALY gain of 0.012 in the Assessment Group's model compared with 0.030 in the analysis by Wilson et al. (2007)
- modelled survival gain compared with no survival gain in Wilson et al.

- lower unit costs and dosing schedule associated with ESAs.

### **4.3 Consideration of the evidence**

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of ESAs, having considered evidence on the nature of anaemia associated with chemotherapy and the value placed on the benefits of ESAs by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

- 4.3.1 The Committee considered the need for treatment in people with anaemia who receive chemotherapy and how it is managed. It heard from the patient expert that symptomatic anaemia is associated with fatigue and the inability to perform everyday tasks; the patient expert explained that when haemoglobin concentration rises, quality of life improves. The Committee understood that it is difficult to distinguish between fatigue from cancer and fatigue resulting from anaemia associated with chemotherapy. The Committee heard from a clinical specialist that standard treatment for anaemia in people having chemotherapy includes blood transfusions and that people now have fewer units of blood because of risks associated with blood transfusion, which, although rare, could worsen quality of life and potentially shorten survival. The clinical specialist explained that ESA treatment is an option for correcting anaemia and reducing the need for a blood transfusion, and that it is started at haemoglobin concentrations generally lower than 90 g/litre and when the patient has symptoms of anaemia. The Committee was aware that this value is lower than the average haemoglobin concentration of 103.8 g/litre reported in the clinical trials assessing ESAs, which is higher than the value of 100 g/litre at which the European Medicine Agency recommends treatment. The Committee was aware that the value of 90 g/litre is also lower than the average haemoglobin concentration of 94 g/litre obtained

when the Assessment Group limited its review to trials treating patients with haemoglobin concentrations of less than 110 g/litre. The clinical specialist highlighted that ESAs lower the need for transfusions, but are not widely used in the UK for treating anaemia in people having chemotherapy, mostly because the recommendations in [NICE technology appraisal guidance 142](#) limit their use. The Committee heard from the patient expert that ESAs are highly valued by patients, because they reduce the need for a blood transfusion and improve quality of life. The Committee understood that the supply of blood transfusions may be limited, and that transfusions may be associated with problems such as iron overload, immune injury and infections. However, it noted the comment from a member of the public during consultation that there have been no shortages of red blood cells for some time, and that transfusions rarely transmit infections. Although the Committee understood that the problems associated with blood transfusions may be rare, it concluded that people with anaemia who have chemotherapy need options for treatment that reduce the need for a blood transfusion and that improve quality of life.

### **Clinical effectiveness**

4.3.2 The Committee considered the clinical effectiveness of ESAs. It heard from the Assessment Group that none of the studies that evaluated ESAs was in line with the current UK marketing authorisations. It was also aware that most of the trials were conducted before the European Medicines Agency revised the marketing authorisations of the ESAs to stipulate a haemoglobin concentration of 100 g/litre or lower at the start of treatment. The Committee was aware that the Assessment Group analysed a subset of studies in which patients were treated with ESAs if their haemoglobin concentration was 110 g/litre or lower in an attempt to match the ESAs' marketing authorisations more closely, while also maintaining a large enough group of studies to generate a reliable

estimate. The Committee concluded that the Assessment Group's analysis reflecting the population closer to the marketing authorisations was relevant to UK clinical practice.

4.3.3 The Committee examined the results of the Assessment Group's systematic review. It noted that the meta-analyses suggested that ESAs increase haemoglobin concentrations, improve haematological responses and reduce the need for a blood transfusion compared with treatment without an ESA. The Committee also considered the results of the subgroup analyses and noted that most of the subgroups included a small number of studies, which limited the interpretation of the results. Having heard from the Assessment Group that the trials were 'flawed', the Committee was concerned about the quality of the included studies and the effect this had on interpreting the results. However, it heard from the Assessment Group that the flaws related mostly to inadequate reporting rather than poor design. The Committee also heard from the clinical specialist that the results for the anaemia-related outcomes were consistent with what clinicians see in practice. The Committee concluded that ESAs were effective in increasing haemoglobin concentrations, improving haematological responses and reducing the need for blood transfusions.

4.3.4 The Committee discussed the overall survival results. It noted that the point estimate for the hazard ratio suggested that ESAs prolong life but that the difference between the treatment arms was not statistically significant at a 0.05 significance level (see sections 4.1.12 and 4.1.16). It heard from the Assessment Group that the trials were not designed to address overall survival, and that the follow-up periods in the trials varied. The Committee understood that the Cochrane review by Tonia et al. (2012) suggested that ESAs increased the risk of death, but noted that this may have been influenced by the fact that the authors did not restrict the

review based on the ESA dose used in the trials (see section 4.1.12). The Committee also understood that the Assessment Group's analysis, which included only studies complying with the licensed ESA starting dose, showed that ESAs have no effect on survival. The Committee heard from the clinical specialist that the main aim of treatment with ESAs is to make people feel better, and not necessarily to extend life. The Committee considered various explanations for the variable survival results associated with ESAs from the trials, including using unlicensed doses of ESAs, promoting tumour growth by improving oxygen supply to the cancer, using ESAs at high starting haemoglobin concentrations, or achieving haemoglobin concentrations that would now be considered too high in light of the revised marketing authorisations. The Committee considered that a survival benefit from ESA treatment could reflect that blood transfusions lower survival, having heard from the clinical specialist that some evidence supports an association between blood transfusions and increased mortality. Based on the balance of the evidence presented, the Committee concluded that it could not assume that ESA treatment either prolonged or shortened survival compared with treatments that did not include ESAs.

- 4.3.5 The Committee considered the health-related quality-of-life results, which showed a statistically significant difference in FACT-F scores between patients treated with an ESA and patients treated without an ESA, as well as the Assessment Group's comments that there were several methodological concerns that may lead to bias. However, the Committee accepted the comments from the clinical specialist and the patient expert that ESA treatment improves people's wellbeing and enables them to perform everyday tasks. It concluded that the available evidence suggests that ESA treatment improves health-related quality of life compared with treatment without ESAs.

4.3.6 The Committee considered the adverse reactions associated with ESAs. It noted from the Assessment Group's meta-analyses that ESAs increased the risks of thromboembolic events, hypertension and pruritus compared with treatment without an ESA. The Committee heard from the clinical specialist that thromboembolic events were the most common serious adverse reactions associated with ESAs, and that these were mostly venous thrombosis and pulmonary embolism. It also heard from the Assessment Group that these adverse reactions occurred rarely in the trials. The Committee considered that the risk of these adverse reactions in the trials might be associated with the high starting and target haemoglobin concentrations in the trials; this was because the Assessment Group's meta-analyses showed that the risks of thromboembolic events and hypertension were slightly lower in the subgroup with haemoglobin concentrations of 110 g/litre or less when starting treatment than in the overall population. It noted that the safety concerns led the European Medicine Agency to revise the marketing authorisation. The Committee concluded that the current evidence suggests that the risks of adverse reactions are lower when ESAs are used in line with their current marketing authorisations.

4.3.7 The Committee considered the relative effectiveness of the different ESAs. It understood that the Assessment Group's subgroup analysis suggested that epoetins increase haemoglobin concentration more than darbepoetin alfa does. However, the Committee recognised that the analysis of darbepoetin contained few studies, that the confidence intervals of the estimates were wide, and that the Assessment Group did not adjust the analyses for multiple testing. The Committee noted that Binocrit and Retacrit are biosimilar medicines, that is, new biological products that are similar to the biological reference medicine (Eprex). The Committee understood that, unlike conventional pharmaceuticals, which can

be copied by chemical synthesis, biopharmaceuticals are complex molecules and are difficult to replicate fully. It also understood that biosimilar products may have a different safety profile from the biological reference medicine biopharmaceutical product. The Committee noted that biosimilar products are regulated by the European Medicines Agency through a centralised procedure, and that the European Medicines Agency's legislation on biosimilars defines the studies needed to demonstrate safety and efficacy to the biological reference medicine. The Committee was aware that making specific recommendations about the safety of a drug falls outside the remit of NICE, and that current advice for prescribing recommends that biopharmaceutical products should be prescribed by brand name. The Committee considered that there was no evidence to suggest differences between the biosimilars and the biological reference medicine, and noted the limitations in the Assessment Group's subgroup analyses comparing different ESAs. The Committee also heard from the clinical specialist that ESAs did not appear to differ in their clinical effectiveness, and that the choice of ESA in clinical practice usually depends on price, and occasionally on difference in dosing frequency. The Committee therefore concluded that it was likely that the ESAs did not differ in clinical effectiveness.

### **Cost effectiveness**

4.3.8 The Committee considered the Assessment Group's economic model and whether its assumptions were appropriate. It noted that the Assessment Group assumed in the model that all ESAs had the same effectiveness. In light of its conclusion that the ESAs did not differ clinically (see section 4.3.7), the Committee concluded that this assumption was reasonable.

4.3.9 The Committee considered whether the modelled treatment duration of 12 weeks was reasonable, noting that the marketing

authorisations allow ESAs to be used up to 4 weeks after chemotherapy ends, and that the treatment duration in the trials varied from 12 to 28 weeks. The Committee considered that this could affect the costs and benefits of ESAs. However, it heard from the clinical specialist that it was common clinical practice to use ESAs for 12 weeks only, that is, during chemotherapy. The Committee noted that the model assumed that haemoglobin returned to normal at concentrations of 120 g/litre, which is in line with the target haemoglobin concentration of 100 to 120 g/litre stated in the marketing authorisations for ESAs. It heard from the clinical specialist that this assumption was reasonable, although some clinicians may prefer to stop treating at the lower end of the target range. The Committee concluded that the treatment duration and haemoglobin concentrations assumed in the model were appropriate.

- 4.3.10 The Committee considered the utility values applied in the economic model. It accepted the Assessment Group's choice to use the study by Harrow et al. (2011) to estimate the short-term utility values. The Committee noted that the sample size was large enough and that although the SF-6D data were collected in women with cancer in the USA, they were valued by the UK general population. It accepted the Assessment Group's mapping of the SF-6D utility to EQ-5D values, in the absence of directly derived EQ-5D data. The Committee was concerned that the Assessment Group did not include disutilities associated with adverse reactions in the QALY calculation given that most adverse reactions occurred more frequently in the ESA arms. However, it recognised that there would be minimal effect on the ICERs given that the adverse reactions in the studies were rare. The Committee heard from the patient expert that it is possible for people to self-administer ESAs at home, which is more convenient for the person and costs the NHS less than hospital attendance for a blood transfusion. The

Committee noted that the benefits from reducing the need for hospital visits were not captured in the QALY calculation. It also considered that there were potential relative health benefits of ESAs associated with avoiding blood transfusions given that any risks from transfusion were not included in the model. The Committee was generally satisfied with the Assessment Group's approach to estimating the utility values but concluded that the QALY gain from ESAs may have been underestimated.

- 4.3.11 The Committee considered the costs used in the model. It noted that the prices of ESAs used in the base case were based on BNF list prices, but that the NHS procures ESAs on a 'price-volume' agreement on a confidential basis with the manufacturers. The Committee noted that NICE's [Guide to the methods of technology appraisal 2013](#) indicates a preference for using nationally available price reductions in the reference-case analysis to reflect the price relevant to the NHS. The Committee concluded that the contract prices were the most relevant prices to the NHS and therefore the appropriate prices on which to base its decision.
- 4.3.12 The Committee considered the scenario assessing the subgroup of people with haemoglobin concentrations of 110 g/litre or lower at the start of ESA treatment. It noted that the ICERs for this scenario were approximately a third lower than the base case (see sections 4.2.14 and 4.2.21). The Committee was aware that this was mostly because the overall survival hazard ratio estimated from the meta-analysis for this subgroup was 0.91 compared with 0.97 used in the base case. However, the Committee agreed that other model parameters specific to this subgroup, such as the lower risks of adverse events and lower haemoglobin concentrations at the start of treatment, contributed to the lower ICERs in this subgroup. The Committee concluded that using ESAs only at haemoglobin

concentrations that reflect the marketing authorisations would slightly reduce the base-case ICERs.

4.3.13 The Committee considered whether ESAs were a cost-effective use of NHS resources and which assumptions it should use to derive the most plausible ICER. The Committee noted that the prices of the drugs and the assumption that ESAs prolong survival most strongly influenced the cost-effectiveness results (see sections 4.2.17 to 4.2.20). The Committee had concluded that there was not enough evidence to suggest a survival gain with ESAs and therefore agreed that the model should incorporate a hazard ratio of 1 instead of 0.97. It also agreed that it was appropriate to use contract prices because these are what the NHS pays. Therefore, the Committee concluded that the scenario assuming equal survival and using contract prices was the most plausible. The Committee noted that the probabilistic ICERs for this scenario were all below £30,000 per QALY gained, although the credible intervals indicated a degree of uncertainty. The Committee considered that including disutilities associated with adverse reactions could increase the ICERs slightly. However, it concluded that the benefits of ESA treatment associated with avoiding blood transfusions (see section 4.3.10) and starting ESA treatment only at haemoglobin concentrations in line with the marketing authorisations (see section 4.3.12) would likely reduce the ICERs. The Committee agreed that the most plausible ICER was below £20,000 per QALY gained, and that ESAs could be considered a cost-effective use of NHS resources and should be recommended as an option for treating anaemia in people with cancer having chemotherapy. The Committee noted that, because it assumed that the ESAs were equally effective, using the ESA with the lowest acquisition cost for a course of treatment would best employ scarce NHS resources. It understood from comments received during consultation that the current tendering process in the NHS for ESAs takes into account

other factors related to the drugs, such as safety, efficacy and dosing frequency. However, the Committee noted that it had already considered these factors in its deliberations. The Committee therefore also recommended that if different erythropoiesis-stimulating agents are equally suitable, the product with the lowest acquisition cost for the course of treatment should be used.

***Summary of Appraisal Committee’s key conclusions***

TAXXX	Appraisal title: Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating anaemia in people with cancer having chemotherapy (including review of TA142)	Section
<b>Key conclusion</b>		
Erythropoiesis-stimulating agents (epoetin alfa, beta, theta and zeta, and darbepoetin alfa) are recommended, within their marketing authorisations, as options for treating anaemia in people with cancer who are having chemotherapy.		1.1
The Committee concluded that ESAs were effective in increasing haemoglobin concentrations, improving haematological responses, reducing the need for blood transfusions and improving health-related quality of life, but that it could not assume that ESA treatment either prolonged or shortened survival compared with treatment without an ESA.		4.3.3, 4.3.4, 4.3.5
The Committee concluded that the contract prices of the ESAs were the most relevant prices to the NHS and that the benefits of ESA treatment associated with avoiding blood transfusions and starting ESA treatment only at haemoglobin concentrations in line with the marketing authorisations would likely reduce the ICERs. The Committee agreed that the most plausible ICER was below £20,000 per QALY gained.		4.3.11, 4.3.13
<b>Current practice</b>		
Clinical need of patients, including the availability of alternative treatments	<p>The Committee heard from the patient expert that symptomatic anaemia is associated with fatigue and the inability to perform everyday tasks. It also heard from the clinical specialists that standard treatment for anaemia in people having cancer treatment includes blood transfusions, which could worsen quality of life and potentially shorten survival.</p> <p>The Committee concluded that people with anaemia who have chemotherapy need options for treatment that reduce the need for a blood transfusion and that improve quality of life.</p>	4.3.1

<b>The technology</b>		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The clinical specialist highlighted that ESAs lower the need for transfusions, but are not widely used in the UK for treating anaemia in people having chemotherapy, mostly because the recommendations in <a href="#">NICE technology appraisal guidance 142</a> limit their use.  The Committee heard from the patient expert that ESAs are highly valued by patients, because they reduce the need for blood transfusions and improve quality of life.	4.3.1
What is the position of the treatment in the pathway of care for the condition?	Not applicable.	
Adverse reactions	The Committee concluded that the current evidence suggests that the risks of adverse reactions are lower when ESAs are used in line with their current marketing authorisations.	4.3.6
<b>Evidence for clinical effectiveness</b>		
Availability, nature and quality of evidence	The Committee heard from the Assessment Group that none of the studies that evaluated ESAs was in line with the current UK marketing authorisations. The Committee was aware that the Assessment Group had attempted to match the ESAs' marketing authorisations more closely while also maintaining a large enough group of studies to generate a reliable estimate.	4.3.2
	The Committee heard from the Assessment Group that the studies were 'flawed' mostly because of inadequate reporting rather than poor design.	4.3.3
Relevance to general clinical practice in the NHS	The Committee was aware that most of the trials were conducted before the European Medicines Agency revised the marketing authorisations of the ESAs to stipulate a haemoglobin concentration of 100 g/litre or lower at the start of treatment, and it appreciated the need for the Assessment Group to maintain enough studies to generate reliable estimates. Therefore, it concluded that the analysis reflecting the population closer to the marketing authorisations was relevant to UK clinical practice.	4.3.2

Uncertainties generated by the evidence	The Committee noted that the point estimate for the hazard ratio suggested that ESAs prolong life but that the difference between the treatment arms was not statistically significant at a 0.05 significance level. It heard from the Assessment Group that the trials were not designed to address mortality, and that the follow-up periods in the trials varied.	4.3.4
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee considered the results of the subgroup analyses and noted that most of the subgroups included a small number of studies, which limited the interpretation of the results.	4.3.3
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that ESAs were effective in increasing haemoglobin concentrations, improving haematological responses, reducing the need for blood transfusions, and improving improves health-related quality of life.	4.3.3, 4.3.5
	The Committee concluded that it could not assume that ESA treatment either prolonged or shortened survival compared with treatments that did not include ESAs.	4.3.4
<b>Evidence for cost effectiveness</b>		
Availability and nature of evidence	The Committee concluded that it was reasonable for the Assessment Group to assume in the economic analysis that all ESAs offer the same effectiveness.	4.3.7, 4.3.8
	The Committee also concluded that the treatment duration and haemoglobin concentrations assumed in the model were appropriate.	4.3.9
	The Committee was generally satisfied with the Assessment Group's approach to estimating the utility values but concluded that the quality-adjusted life years (QALY) gain with ESAs may have been underestimated.	4.3.10
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee was concerned that the Assessment Group did not include disutilities associated with adverse reactions in the QALY calculation given that most adverse reactions occurred more frequently in the ESA arms. However, it recognised that there would be minimal effect on the incremental cost-effectiveness ratios (ICERs) given that the adverse reactions in the studies were rare.	4.3.10

	The Committee concluded that there was not enough evidence to suggest a survival gain with ESAs and therefore agreed that the model should incorporate a hazard ratio of 1 instead of 0.97.	4.3.13
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The Committee concluded that the QALY gain with ESAs may have been underestimated given that the potential benefits of ESAs associated with avoiding blood transfusions and reducing the need for hospital visits were not captured in the QALY calculation.	4.3.10
Are there specific groups of people for whom the technology is particularly cost effective?	The Committee concluded that using ESAs only at starting haemoglobin concentrations that reflect the marketing authorisations would slightly reduce the base-case ICERs.	4.3.12
What are the key drivers of cost effectiveness?	The Committee noted that the prices of the drugs and the assumption that ESAs prolong survival most strongly influenced the cost-effectiveness results.	4.3.13
Most likely cost-effectiveness estimate (given as an ICER)	The Committee concluded that the scenario assuming equal survival and using contract prices was the most plausible. It noted that the probabilistic ICERs for this scenario were all below £30,000 per QALY gained and that the benefits of ESA associated with avoiding blood transfusions and starting ESA treatment only at haemoglobin concentrations in line with the marketing authorisations would likely reduce the ICERs. The Committee agreed that the most plausible ICER was below £20,000 per QALY gained.	4.3.13
<b>Additional factors taken into account</b>		
Patient access schemes (PPRS)	None.	–
End-of-life considerations	Not applicable	–
Equalities considerations and social value judgements	No equality issues relevant to the Committee's recommendations were raised.	–

## 5 Implementation

- 5.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 5.2 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has anaemia associated with cancer treatment and the doctor responsible for their care thinks that erythropoiesis-stimulating agents is the right treatment, it should be available for use, in line with NICE’s recommendations.
- 5.3 The NHS procures ESAs on a ‘price-volume’ agreement on a confidential basis with the manufacturers. The contract prices used for the decision-making in this appraisal represent the latest tenders to London hospitals provided for this appraisal by the Commercial Medicines Unit and the South East England Specialist Pharmacy Services to NICE. Any enquiries from NHS organisations about the contract prices used in this appraisal should be directed to the Commercial Medicines Unit and the South East England Specialist Pharmacy Services [NICE to add details at time of publication].
- 5.4 NICE has developed [tools](#) [link to <http://guidance.nice.org.uk/TAXXX>] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]
- Slides highlighting key messages for local discussion.

- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

## 6 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the [NICE website](#).

- [Epoetin alfa, epoetin beta and darbepoetin alfa for cancer treatment-induced anaemia](#). NICE technology appraisal guidance 142 (2008).

## 7 Review of guidance

- 7.1 The guidance on this technology will be considered for review 3 years after publication of this guidance. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Dr Amanda Adler

Chair, Appraisal Committee

June 2014

## **8 Appraisal Committee members, guideline representatives and NICE project team**

### **8.1 *Appraisal Committee members***

The Appraisal Committees are standing advisory committees of NICE. 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. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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.

#### **Dr Amanda Adler (Chair)**

Consultant Physician, Addenbrooke's Hospital

#### **Professor Ken Stein (Vice Chair)**

Professor of Public Health, University of Exeter Medical School

#### **Dr Ray Armstrong**

Consultant Rheumatologist, Southampton General Hospital

#### **Dr Jeff Aronson**

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

**Professor John Cairns**

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

**Mr Matthew Campbell-Hill**

Lay member

**Mr Mark Chapman**

Health Economics and Market Access Manager, Medtronic UK

**Professor Imran Chaudhry**

Lead Consultant Psychiatrist and Deputy Associate Medical Director, Lancashire Care NHS Foundation Trust

**Dr Lisa Cooper**

Echocardiographer, Stockport NHS Foundation Trust

**Dr Maria Dyban**

GP, Cardiff

**Mr Robert Hinchliffe**

HEFCE (Higher Education Funding Council for England) Clinical Senior Lecturer in Vascular Surgery and Honorary Consultant Vascular Surgeon, St George's Vascular Institute

**Dr Neil Iosson**

Locum GP

**Ms Anne Joshua**

Pharmaceutical Advisor NHS 111/NHS Pathways

**Dr Miriam McCarthy**

Consultant, Public Health, Public Health Agency, Northern Ireland

**Professor Ruairidh Milne**

Director of Strategy and Development and Director for Public Health

Research, National Institute for Health Research (NIHR) Evaluation, Trials and Studies Coordinating Centre, University of Southampton

**Dr Peter Norrie**

Principal Lecturer in Nursing, De Montfort University

**Mr Christopher O'Regan**

Head of Health Technology Assessment and Outcomes Research, Merck Sharp and Dohme

**Dr Sanjeev Patel**

Consultant Physician and Senior Lecturer in Rheumatology, St Helier University Hospital

**Dr John Pounsford**

Consultant Physician, Frenchay Hospital, Bristol

**Dr Danielle Preedy**

Lay Member

**Dr John Rodriguez**

Assistant Director of Public Health, NHS Eastern and Coastal Kent

**Mr Alun Roebuck**

Consultant Nurse in Critical and Acute Care, United Lincolnshire NHS Trust

**Mr Cliff Snelling**

Lay Member

**Mr David Thomson**

Lay Member

**Professor Andrew Stevens**

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

**Dr Nerys Woolacott**

Senior Research Fellow, Centre for Health Economics, University of York

**Dr Nicky Welton**

Senior Lecturer in Biostatistics/Health Technology Assessment, University of Bristol

**8.2 NICE project team**

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**Nwamaka Umeweni and Ian Watson**

Technical Leads

**Zoe Charles and Nwamaka Umeweni**

Technical Advisers

**Jeremy Powell**

Project Manager

**9 Sources of evidence considered by the Committee**

A. The assessment report for this appraisal was prepared by the Peninsula Technology Assessment Group, University of Exeter:

- Crathorne L, Huxley N, Haasova M et al. The effectiveness and cost-effectiveness of erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating cancer-treatment induced anaemia (including review of TA142): a systematic review and economic model, January 2014

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document

(ACD). Organisations listed in I, II and III were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I. Manufacturers/sponsors:

- Amgen
- Hospira
- Janssen
- Roche
- Sandoz

II. Professional/specialist and patient/carer groups:

- British Society for Haematology
- Leukaemia Cancer Society
- Leukaemia CARE
- Myeloma UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- Target Ovarian Cancer

III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

IV. Commentator organisations (without the right of appeal):

- Cochrane Haematological Malignancies Group
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland

- Healthcare Improvement Scotland
- Hospital Information Services (Jehovah's Witnesses)
- Medicines and Healthcare products Regulatory Agency
- Medical Research Council (MRC) Clinical Trials Unit

C. The following individuals were selected from clinical specialist and patient expert nominations from the 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 erythropoiesis-stimulating agents by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Tim Littlewood, Consultant, Oxford University Hospitals, nominated by the Royal College of Pathologists – clinical specialist
- Ken Campbell, Scientific and Medical Education Specialist, Myeloma UK, nominated by Myeloma UK – patient expert

D. Representatives from the following manufacturers/sponsors attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy. They were also invited to comment on the ACD.

- Amgen
- Sandoz