NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Overview

Erythropoiesis-stimulating agents (epoetin and darbepoetin) for treating cancer-treatment induced anaemia (including review of TA 142)

This overview is a summary of:

- the evidence and views submitted by the manufacturers, the consultees and their nominated clinical specialists and patient experts and
- the assessment report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available before comments on the assessment report have been received.

Key issues for consideration

Clinical effectiveness

- There is consistent evidence that erythropoiesis-stimulating agents (ESAs) improve anaemia-related outcomes such as improving haemoglobin concentrations and reducing the need for red blood cell transfusion. However, whether ESAs prolong survival is less clear - the Assessment Group's meta-analysis suggested an increase in survival which was not statistically significant, whereas previous reviews have shown either no difference in survival, or lower survival associated with ESAs (see section 4.13). What is the Committee's view on the likelihood of a survival benefit with ESA treatment compared with no ESA treatment? Is it reasonable to assume a treatment benefit during chemotherapy? After chemotherapy, and, if so, for how long?
- The majority of trials treat with ESAs for 12 weeks. Does this reflect treatment in England? Does treatment with ESAs continue after chemotherapy?

- Trial evidence suggests that ESAs increase the risk of thromboembolic events, hypertension and pruritus. What is the nature of the thromboembolic events? To what extent do the advantages of treatment outweigh the risks?
- The Assessment Group stated that none of the identified studies evaluated ESAs entirely in line with their marketing authorisations which stipulate a haemoglobin concentration at which to start, and at which to stop treatment. Therefore the Assessment Group focused on studies evaluating the ESAs at their licensed starting dose, irrespective of other aspects of marketing authorisation. Does the Committee consider the Assessment Group's analyses of the ESAs to be generalisable to the population covered by the marketing authorisations?
- The recommendation in NICE technology appraisal 142 restricted the use of erythropoietin analogues to women receiving platinum-based chemotherapy for ovarian cancer and to people who cannot receive blood transfusions and who have profound anaemia that is likely to impact on survival. The Assessment Group identified one study evaluating ESAs use in women with ovarian cancer receiving platinum-based chemotherapy (see section 4.18). It was unable to identify any trials that evaluated the use of ESAs in people who cannot receive blood transfusion. What is the Committee's view on the relevance of these 2 subgroups? Does the Committee consider that the effectiveness of the ESAs differs in these groups compared with the overall population?
- What is the Committee's view on the potential equality issue raised by consultees regarding people who are unable to receive blood transfusion for religious reasons (the Jehovah's Witness group)?

Cost effectiveness

- Survival gain was a major driver of the cost-effectiveness results. Is it appropriate to assume a survival benefit from ESAs in the economic analysis?
- A second key driver of the cost-effectiveness results was the price of the ESAs (published list prices compared with wholesale acquisition prices). Which prices does the Committee consider to be most appropriate for the economic analysis?

- The Assessment Group performed scenario analyses to explore the impact of changes in assumptions for overall survival and the price of ESAs. Which analysis does the Committee consider to be most plausible?
- The Assessment Group extrapolated overall survival using an exponential distribution in the base case (see section 6.7) and alternative distributions in scenario analyses (sections 6.22 and 6.23). Which analysis does the Committee consider to be most appropriate?
- What is the Committee's view on the utility values used in the model give that:
  - the short-term utility values were derived from women with cancer who may not necessarily be receiving cancer treatment and may not be receiving ESAs
  - the short-term utility values were valued by the US general public, rather than the UK public
  - the long term utility value of 0.76 is highly uncertain due to lack of data.
- The Assessment Group did not include disutiites associated with adverse events in the model because the included studies did not adequately define and report adverse events. What is the Committee's view on the potential impact of including disutilites associated with adverse events in the QALY calculation?
- The Assessment Group assumed in its model that treatment with ESA lasts for 12 weeks only (during active chemotherapy) because most of the studies in the meta-analysis (13 of 23) reported a 12-week treatment period. What is the Committee's view on the impact of this assumption, given that it is possible for ESA treatment to continue up to 4 weeks after chemotherapy?

1 Background: clinical need and practice

1.1 Anaemia is defined as a reduction of the haemoglobin concentration, red cell count, or packed cell volume below normal levels. Red blood cells carry oxygen to tissues. The World Health Organization defines anaemia as a haemoglobin concentration of less than 12 g/dl in women and less than 13 g/dl in men. Erythropoiesis, the production of red blood cells, occurs in the bone marrow, requires iron, and is stimulated by the hormone erythropoietin produced in the kidney. The cause of anaemia is

usually multifactorial related to the patient, disease, or treatment. More than 50% of people with cancer will be anaemic regardless of the treatment received and approximately 20% of people receiving chemotherapy will require red blood cell transfusion. Cancer treatment can suppress the production of red blood cells in the bone marrow temporarily, and cumulative damage can occur over several chemotherapy cycles. Once cancer treatments are stopped, a period of normalisation is likely, during which the haemoglobin may return to pre-treatment concentrations. People treated with platinum-based chemotherapy frequently develop anaemia and need transfusion.

1.2 Anaemia can compromise treatment, contribute to the progression of cancer and reduce survival. It is associated with symptoms, which can affect quality of life. Mild to moderate anaemia can typically cause headache, palpitations, tachycardia and shortness of breath. Chronic anaemia can result in organ damage. Severe fatigue is the most common symptom, and can lead to being unable to perform everyday tasks.

1.3 Approximately 60% of people with solid tumours who receive chemotherapy become anaemic with a haemoglobin concentration of less than 11 g/dl. The incidence of anaemia is highest in people with lung cancer (71%) and gynaecological cancer (65%), as these cancers currently involve treatment with platinum-based chemotherapy. The proportion of people who require red blood cell transfusion varies from 47 to 100% depending on the cumulative dose of platinum chemotherapy received as well as age, disease stage and pre-treatment haemoglobin level. For haematological cancers, about 75% of people with multiple myeloma are anaemic at diagnosis and 70% of people with lymphoma are anaemic by cycles 3 to 4 of their chemotherapy.

1.4 Cancer treatment-induced anaemia is managed by adjusting the cancer treatment regimen, iron supplementation and blood transfusion in cases of severe anaemia. Problems related to blood transfusion include the limited

supplies, iron overload, immune injury, viral and bacterial infections. NICE technology appraisal guidance 142 recommends erythropoietin analogues in combination with intravenous iron as an option to manage cancer treatment-induced anaemia in women receiving platinum-based chemotherapy for ovarian cancer who have symptomatic anaemia with a haemoglobin concentration of 8 g/100 ml or lower. Erythropoietin analogues may also be considered for people who cannot receive blood transfusions and who have profound cancer treatment-related anaemia that is likely to have an impact on survival.

2 The technologies

2.1 Epoetin and darbepoetin are erythropoiesis-stimulating agents (ESAs).

Epoetins

2.2 Epoetin alfa, beta, theta and zeta are recombinant human erythropoietin analogues used to shorten the period of symptomatic anaemia in patients receiving cytotoxic chemotherapy. They are recommended for use at haemoglobin concentrations of 10 g/dl or lower, with target values up to 12 g/dl.

Epoetin alfa

2.3 Epoetin alfa (Eprex, Janssen-Cilag) and (Binocrit, Sandoz) have UK marketing authorisations to treat anaemia and to reduce 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 (e.g. cardiovascular status, pre-existing anaemia at the start of chemotherapy). Binocrit is a biosimilar medicine referenced to Eprex.

2.4 The summary of product characteristics lists the following adverse reactions for Eprex and Binocrit: headache, deep vein thrombosis, hypertension, pulmonary embolism, nausea, diarrhoea, vomiting, rash, arthralgia, pyrexia and influenza-like illness. Stroke is also commonly

observed with Binocrit. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.5 Eprex and Binocrit are available in pre-filled syringes at net prices of £5.53 and £5.09 per 1000 units respectively (excluding VAT; 'British national formulary' [BNF] edition 66). 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

2.6 Epoetin beta (NeoRecormon, Roche Products) has a UK marketing authorisation to treat symptomatic anaemia in adult patients with non-myeloid malignancies who are receiving chemotherapy.

2.7 The summary of product characteristics lists the following adverse reactions for epoetin beta: hypertension, thromboembolic event and headache. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.8 Epoetin beta is available in a pre-filled syringe at a net price of £3.51 per 500 units (excluding VAT; 'British national formulary' [BNF] edition 66). 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

2.9 Epoetin theta (Eporatio, Teva UK) has a UK marketing authorisation to treat symptomatic anaemia in adult patients with non-myeloid malignancies who are receiving chemotherapy

2.10 The summary of product characteristics lists the following adverse reactions for epoetin theta: shunt thrombosis (for patients on

hemodialysis), headache, hypertension, skin reactions, arthralgia and influenza-like illness. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.11 Epoetin theta is available in a pre-filled syringe at a net price of £5.99 per 1000 units (excluding VAT; 'British national formulary' [BNF] edition 66). 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

2.12 Epoetin zeta (Retacrit, Hospira UK) is a biosimilar medicine referenced to Eprex which contains epoetin alfa. It has a UK marketing authorisation to treat anaemia and to reduce 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 (e.g. cardiovascular status, pre-existing anaemia at the start of chemotherapy)

2.13 The summary of product characteristics lists the following adverse reactions for epoetin zeta: headache, stroke, dizziness, deep vein thrombosis, increase in blood pressure, pulmonary embolism, non-specific skin rashes, joint pains, flu-like symptoms, feeling of weakness, tiredness and clotting of an artificial kidney. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.14 Epoetin zeta is available in a pre-filled syringe at a net price of £5.66 per 1000 units (excluding VAT; 'British national formulary' [BNF] edition 66). 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

2.15 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 to treat symptomatic anaemia in adult cancer patients with non-myeloid malignancies who are receiving chemotherapy. It is recommended for use at haemoglobin concentrations of 10 g/dl or lower, with target values up to 12 g/dl.

2.16 The summary of product characteristics lists the following adverse reactions for darbepoetin alfa: hypersensitivity, hypertension, thromboembolic events (including pulmonary embolism), rash/erythema, oedema and injection site pain. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.17 Darbepoetin alfa is available in a pre-filled syringe at a net price of £14.68 per 10 micrograms (excluding VAT; 'British national formulary' [BNF] edition 66). 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.

Summary of the technologies

Table 1 Summary description of technologies

Non-proprietary name	Epoetin alfa	Epoetin alfa	Epoetin beta	Epoetin theta	Epoetin zeta	Darbepoetin alfa
Proprietary name	Eprex	Binocrit	NeoRecormon	Eporatio	Retacrit	Aranesp
Manufacturer	Janssen-Cilag	Sandoz	Roche Products	Teva UK	Hospira UK	Amgen
Start haemoglobin concentration	≤10 g/dl	≤10 g/dl	≤10 g/dl	≤10 g/dl	≤10 g/dl	≤10 g/dl
Target haemoglobin concentration	10 to 12 g/dl	10 to 12 g/dl	10 to 12 g/dl	10 to 12 g/dl	10 to 12 g/dl	10 to 12 g/dl
Dose	150 units/kg body weight 3 times weekly or 450 units/kg body weight once a week	150 units/kg body weight 3 times weekly or 450 units/kg body weight once a week	450 units/kg body weight once a week	20,000 units once a week	150 units/kg body weight 3 times weekly or 450 units/kg body weight once a week	500 micrograms (6.75 micrograms/ kg body weight) once every 3 weeks or 2.25 micrograms/ kg body weight once a week
Acquisition cost (BNF edition 66)	1000 units pre-filled syringe = £5.53	1000 units pre-filled syringe = £5.09	500 units pre-filled syringe = £3.51	1000 units pre-filled syringe = £5.99	1000 units pre-filled syringe = £5.66	10 micrograms pre-filled syringe = £14.68

3 Remit and decision problem

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of erythropoiesis-stimulating agents (epoetin and darbepoetin) within their licensed indications for treating cancer-treatment induced anaemia[1].

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol
Population	• People receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma, and at risk of transfusion as assessed by the patient's general status (e.g. cardiovascular status, pre-existing anaemia at the start of chemotherapy) • People with non-myeloid malignancies who are receiving chemotherapy	
Intervention	• Epoetin alfa, beta, theta and zeta • Darbepoetin alfa	
Comparators	• Best supportive care (including adjustments to the cancer treatment regimen, blood transfusion and iron supplementation) • The interventions will be compared with each other in line with their marketing authorisations	
Outcomes	• Haematological response to treatment • Need for blood transfusion • Tumour response (time to cancer progression) • Overall survival • Adverse effects of treatment • Health-related quality of life	
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	

[1] This appraisal includes a review of Technology Appraisal No. 142, May 2008, 'Epoetin alfa, epoetin beta and darbepoetin alfa for cancer treatment-induced anaemia

4 Clinical-effectiveness evidence

4.1 The Assessment Group identified 23 randomised controlled trials (RCTs) evaluating the effectiveness and safety of ESAs for treating cancer treatment-related anaemia. These included 16 studies from the previous review by Wilson et al. (2007) used in NICE technology appraisal guidance 142. The Assessment Group stated that none of the identified studies evaluated ESAs entirely in line with their marketing authorisations. Therefore the Assessment Group's review focused only on studies that evaluated the interventions at a starting dose reflecting the current license, whether or not the studies treated participants at concentrations of hemoglobin in line with of the license.

4.2 Of the 23 included studies, 13 studies compared ESAs plus standard care with placebo plus standard care. Of these:

- 4 studies assessed epoetin alfa;
- 4 studies assessed darbepoetin alfa;
- 2 studies assessed epoetin beta;
- 1 study assessed epoetin theta;
- 1 study was a 3-arm trial which assessed epoetin beta and epoetin theta compared with placebo;
- 1 study, the Assessment Group could not determine which ESA was used.

The remaining 10 studies compared ESAs plus standard care with standard care alone:

- 5 studies assessed epoetin alfa;
- 2 studies assessed epoetin beta;
- 1 study assessed darbepoetin alfa;
- 2 studies, the Assessment Group could not determine which ESA was used.

The Assessment Group noted the lack of head-to-head RCT evidence but did not specifically address the relative effectiveness of different ESAs.

4.3 The Assessment Group stated that it was difficult to assess study quality in most of the trials which omitted important information. It indicated that all the trials were flawed. In particular, it noted that no trial clearly reported methods related to allocating patients to treatments.

4.4 In the majority of the trials, erythropoietin therapy was given to patients over the course of chemotherapy, and in some trials, continued for four weeks after chemotherapy. The average duration of treatment with erythropoietin was 12 weeks, ranging from 12 to 28 weeks. Concomitant treatments including granulocyte colony-stimulating factor, iron, and red blood cell transfusion were allowed in some of the trials. Iron supplementation was given in 16 studies, either orally or intravenously; and in 1 study, iron supplementation was given only to patients receiving erythropoietin therapy.

4.5 Patient's age in the trials ranged from 18 to 92 years. There was an equal distribution of men and women in most of the trials except in trials of gynaecological and breast malignancies. However in the study by Dunphy et al. (1999) comprising of head, neck and lung tumours, 92% of the participants in the ESA group were men compared with an equal distribution of men and women in the control group. The types of malignancy included in the trials varied (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 (6 trials) and chemotherapy plus radiotherapy (1 trial). In 6 studies, the type of chemotherapy used was not reported.

Table 2 Summary of included studies

Study, year	n	Agent	Control	Malignancy	Treatment	Outcomes	Multiple publications identified
Wilson and colleagues (2004 [HTA]) included studies meeting inclusion criteria for the PenTAG review							
Abels, 1993[54]	413[a]	Epoetin alfa	Placebo	Haem[e]	Chemo: mixed	HaemR, Hct, RBCT, HRQoL[b], AE[b]	Abels, 1996; Case, 1993; Henry 1994, Henry, 1995
Aravantinos, 2003[63]	47	Epoetin alfa	Standard	Solid	Chemo: plat	Hb, HCT, patients' RBCT	NA
Boogaerts, 2003[52]	262	Epoetin beta	Standard	Solid & haem[e]	Chemo: NR	HaemR, Hb, RBCT, HRQoL	Coiffier, 1999 (abstract)
Dammacco, 2001[64]	145	Epoetin alfa	Placebo	Haem[e]	Chemo: mixed[d]	HaemR, Hb, RBCT, HRQoL, AE	NA
Del Mastro, 1997[65]	62	rHuEPO[b]	Standard	Solid (breast)	Chemo: non-plat	Hb, RBCT, HRQoL, AE	NA
Dunphy, 1999[66]	30	rHuEPO[b]	Standard	Solid (head & neck, lung)	Chemo: mixed	Hb, RBCT	NA
Hedenus, 2002[49]	33[e]	Darb alfa	Placebo	Haem[e]	Chemo: NR	HaemR, Hb, RBCT, AE	NA
Hedenus, 2003[16]	349	Darb alfa	Placebo	Haem[e]	Chemo: NR	HaemR, RBCT, AE, HRQoL	Littlewood, 2006
Kotasek, 2003[46]	249	Darb alfa	Placebo	Solid	Chemo: NR	HaemR, Hb, RBCT, HRQoL	NA
Kurz, 1997[67]	35	Epoetin alfa	Placebo	Solid (cervix, ovary, uterus)	Chemo: mixed	HaemR, RBCT, HRQoL, AE	NA
Littlewood, 2001[68]	375	Epoetin alfa	Placebo	Mixed	Chemo: non-plat	HaemR, Hb, RBCT, HRQoL, AE	Aapro, 2004; Bajetta, 2004; Patrick 2003
Osterborg, 2002, 2005[69,70]	349	Epoetin beta	Placebo	Haem[e]	Chemo: non-plat	HaemR, Hb, RBCT, HRQoL, AE	Osterborg, 2005 (survival data from Osterborg, 2002))
Silvestris, 1995[71]	54	Epoetin alfa	Standard	Haem[e]	Chemo: NR	HaemR, Hb, AE	NA
Ten Bokkel, 1998[47]	122	Epoetin beta	Standard	Solid (ovary)	Chemo: plat	Patients' RBCT, AE	NA

Study, year	n	Agent	Control	Malignancy	Treatment	Outcomes	Multiple publications identified
Thatcher, 1999[48]	130	Epoetin alfa	Standard	Solid (SCLC)	Chemo: mixed	Hb, Patients' RBCT, HRQoL, AE	NA
Vansteenkiste, 2002[72]	314	Darb alfa	Placebo	Solid (lung)	Chemo: plat	HaemR, Hb, RBCT, HRQoL, AE, disease progression, survival	Vansteenkiste, 2004
Study characteristics: PenTAG review update 2004 to July 2007							
Grote, 2005[73]	224	Epoetin alfa	Placebo	Solid (SCLC)	Chemo: mixed	Hb, RBCT, TR; survival; AE	NA
Moebus, 2013[62]	643	Epoetin alfa	Standard	Solid (breast)	Chemo: non-plat	Hb, RBCT, HRQoL, survival, AE	NA
Ray-Coquard, 2009[74]	218	Epoetin alfa	Standard	Mixed	Chemo: NR	RBCT, OS, HRQoL, AE	NA
Strauss, 2008[75]	74	Epoetin beta	Standard	Solid (cervix)	Chemo + Radio	Hb RBCT, TR, survival, AE	NA
Tjulandin, 2010[45]	223	Epetin theta Epoetin beta	Placebo	Solid	Chemo: plat	HaemR, Patients' RBCT, HRQoL, AE	NA
Tjulandin, 2011[76]	186	Epoetin theta	Placebo	Mixed	Chemo: non-plat	HaemR, Patients' RBCT, HRQoL, AE	NA
Untch, 2011a, b[77,78]	733	Darb alfa	Standard	Solid (breast)	Chemo: non-plat	Hb, pathological response, disease progression, survival, AE	NA

Key: AE, adverse event; Darb, darbepoetin; HaemR, haematopoietic response; Hb, haemoglobin; HRQoL, health-related quality of life; NR, not reported; OS, overall survival; plat, platinum-based chemotherapy; RBCT, red blood cell transfusion; refs, references; rHuEPO, recombinant human erythropoietin; SCLC, small-cell lung cancer; TR, tumour response

Notes: (a) Study population included patients not receiving chemotherapy (n=124); beyond the scope for the current review; **(b)** Outcomes reported for all participants (i.e. includes patients not receiving chemotherapy); **(c)** Assumed to epoetin alfa or epoetin beta based on date of study and dose administered; **(d)** majority of participants reported to be on non-platinum chemotherapy; **e** Dose-response study other doses of darbepoetin alfa included; **(e)** specifically haematological non-myeloid malignancies (chronic lymphocytic leukaemia; non Hodgkin's lymphoma; Hodgkin's disease and multiple myeloma within these studies)

Source: assessment report (table 10, page 69-70)

4.6 The outcomes from the included studies were grouped into 4 categories:

- Anaemia outcomes: This includes:
  - mean haemoglobin change (defined as a change in haemoglobin concentrations from baseline until the end of the treatment period);
  - haematological response (defined as the proportion with an increase in haemoglobin concentration of 2 g/dl or more, or as an increase in haematocrit of 6% or more);
  - red blood cell transfusion requirements (including number of patients transfused, number of units transfused per patient and number of units transfused per average patient, that is, including patients not requiring transfusion)
- Malignancy outcomes: This includes complete tumour response, overall survival and on-study mortality.
- Adverse events
- Health-related quality of life

4.7 The Assessment Group pooled the results of the individual trials in meta-analyses using a random-effects model. All the erythropoietin analogues were considered together and classed as the ESA group, whereas the non-ESA group included patients randomised to either placebo and standard care or standard care alone. The Assessment group also conducted sensitivity analyses for each outcome using fixed-effects meta-analyses, and used this to compare the results with the Cochrane review by Tonia et al. (2012) and the review by Wilson et al. (2007). Where data were available, the Assessment Group conducted subgroup analyses for haemoglobin concentration at study entry, target haemoglobin, type of malignancy, whether or not a patient has ovarian cancer, type of cancer treatment, type of ESA received (that is, short-lasting epoetin or long-lasting darbepoetin), iron supplementation, duration

of ESA treatment and trial design (placebo plus standard care or standard care alone). However it indicated that the small number of studies included for each subgroup would introduce uncertainties in the subgroup results.

Outcomes related to anaemia

4.8 The random-effects analysis of mean haemoglobin change included 16 trials (n=3170) and showed a weighted mean difference (WMD) between the ESA group and the non-ESA group of 1.59 g/dl from baseline to 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 all individual trials indicated a ESAs increased haemoglobin. The fixed-effects analysis also showed a difference in haemoglobin change in favour of the ESA group, but with a high degree of heterogeneity (WMD 1.49 g/dl, 95% CI 1.37 to 1.60; I^2=75.9%, p<0.001). Although the effect of ESAs in increasing haemoglobin concentration was consistent across all subgroups, there were statistically significant differences between the types of ESA and between chemotherapy treatments. The analysis showed that epoetin treatment offered greater benefits compared to longer lasting darbepoetin treatment and that the ESAs were more effective in the studies with mixed chemotherapy than the studies with other types of cancer treatment.

4.9 Using a random-effects model and meta-analysing 10 trials (n=2228), the Assessment Group reported a risk ratio (RR) for haematological response in favour of ESA treatment of 3.29 (95% CI 2.84 to 3.81) compared with no ESA treatment, and when using a fixed-effects model was 3.41 (95% CI 2.96 to 3.92). All the individual studies indicated a beneficial effect of ESA treatment with no heterogeneity (I^2=6.4%, p=0.383).

4.10 Fewer patients randomised to ESA treatment than patients randomised to treatments other than ESA (554 of 2480 compared with 835 of 2299 patients) required blood transfusion in the 22 studies that assessed transfusion requirements. 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. The meta-analysis found no heterogeneity (I^2=10.5%, p=0.315) and all but 1 study indicated a beneficial effect of ESA treatment.

4.11 In addition to evaluating whether patients required blood transfusions, the Assessment Group evaluated whether there was a difference in how many units of blood a transfused patient required. The Assessment Group reported that based on 10 studies evaluating 1,920 patients, patients randomised to ESA compared to patients not randomised to ESA required 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 observed moderate heterogeneity between trials (I^2=59.3%, p=0.006), all but 1 study indicated that patients using ESA required less blood. The effect of ESA in reducing the number of units of blood transfused was consistent across all subgroups, except for the subgroup characterised by having participated in studies with duration of treatment of 17 to 20 weeks (WMD 0.10, 95% CI -0.59 to 0.79).

Table 3 Summary of outcomes related to anaemia

	Wilson, 2007[b]	**Tonia, 2012[b]**	**PenTAG, 2013[b]**	**PenTAG, 2013[c]**
Anaemia-related outcomes				
Change in Hb (haemoglobin) in g/dl. (WMD greater than zero indicates a benefit with	WMD 1.63 95% CI 1.46−1.80 10 trials, n=1,620	WMD 1.57 95% CI 1.51−1.62 75 trials, n=11,609	WMD 1.49 95% CI 1.37−1.60 18 trials, n=3,170	WMD 1.59 95% CI 1.33−1.84 18 trials, n=3,170

ESAs)				
Haematological response - % achieving an increase in Hb of ≥ 2 g/dl (yes vs. no)	RR 3.40 95% CI 3.01−3.83 21 trials, n=3,740	RR 3.39 95% CI 3.10−3.71 46 trials, n=6,413	RR 3.41 95% CI 2.96−3.92 12 trials, n=2,228	RR 3.29 95% CI 2.84−3.81 12 trials, n=2,228
Red blood cell transfusion (yes vs. no)	RR 0.63 95% CI 0.58−0.67 35 trials, n=5,564	RR 0.65 95% CI 0.62−0.68 88 trials, n=16,093	RR 0.62 95% CI 0.58−0.67 24 trials, n=4,799	RR 0.63 95% CI 0.57−0.69 22 trials, n=4,799
Units of red blood cells transfused. (WMD less than zero indicates a benefit with ESAs)	WMD -1.05 95% CI 1.32−0.78 14 trials, n=2,353	WMD -0.98 95% CI 1.17−0.78 25 trials, n=4,715	WMD -0.64 95% CI 0.79−0.48 11 trials, n=1,920	WMD -0.87 95% CI 1.28−0.46 11 trials, n=1,920

Key: CI, confidence interval; RR, relative risk; WMD, weighted mean difference

Notes: (a) change from baseline to end of study; **(b)** fixed effects (Mantel-Haenzel); **(c)** random effects (Der-Simonian Laird), haematological response was defined as the proportion of participants with an increase in Hb concentration of 2 g/dl or more, or as an increase in haematocrit of six percentage points or more; **(d)** the number of trials includes multiple experimental arms for some studies.

Source: assessment report (table 19, page 109)

Outcomes related to malignancy

4.12 Whether or not a patient's cancer responded to treatment was measured as 'complete tumour response' in 7 studies comprising 1909 patients. Randomisation to the EPO group, compared with the non-EPO group, was associated with a pooled risk ratio of 1.10 (95% CI 0.86 to 1.41) for complete tumour response. The Assessment Group did not find heterogeneity between the trials; however, the direction of effect varied between trials. The fixed-effects analysis showed similar results (RR 1.20, 95% CI 0.85 to 1.71). The Assessment Group highlighted that the review by Wilson et al. (2007) showed that ESAs compared with no ESAs 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).

4.13 To assess whether EPOs prolonged or shortened overall survival, the Assessment Group extracted the majority of the data from the Cochrane review by Tonia et al. (2012), where the reported hazard ratios were based on individual patient data. The Assessment Group's meta-analysis included 18 trials comprising 4454 patients, where 818 out of 2317 patients in the ESA group and 744 out of 2137 patients in the non-ESA group had died. The pooled hazard ratio (HR) for the association of treatment with an ESA and death was 0.97 (95% CI 0.83 to 1.13) and there was moderate heterogeneity between the trials (I^2=42.4%, p=0.03). The fixed-effects analysis showed a similar result of no difference in survival (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 review by Tonia et al. (2012) which reported a detrimental effect of ESAs on survival (HR 1.05, 95% CI 1.00 to 1.11). The Assessment Group emphasised that its analysis only included studies complying with the licensed ESA starting dose, whereas the inclusion criteria for the Cochrane review did not apply any restrictions to the ESA dose.

4.14 The Assessment Group's meta-analysis of mortality during the period of the study included 14 studies comprising 2967 patients. Overall, the Assessment Group reported no difference in mortality (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 mortality (HR 0.87, 95% CI 0.70 to 1.09); whereas the review by Tonia et al. (2012) showed that treatment with ESA increased the risk of death (HR 1.17, 95% CI 1.03 to 1.29).

Table 4 Summary of outcomes related to malignancy

	Wilson, 2007[a]	Tonia, 2012[a]	PenTAG, 2013[a]	PenTAG, 2013[b]
Malignancy-related outcomes				
Tumour response	RR 1.31 95% CI 1.08−1.60 9 trials, n=1,260	RR 1.02 95% CI 0.98−1.06 19 trials, n=5,012	RR 1.20 95% CI 0.85−1.71 7 trials, n=1,909	RR 1.10 95% CI 0.86−1.41 7 trials, n=1,909
Overall survival	HR 1.03 95% CI 0.92−1.16 28 trials, n=5,308	HR 1.05 95% CI 1.00−1.11 76 trials, n=18.754	HR 0.98 95% CI 0.89−1.08 18[c] trials, n=4,399	HR 0.97 95% CI 0.83−1.13 18[c] trials, n=4,454
Mortality during the study period	NR	HR 1.17 95% CI 1.03−1.29 64 trials, n=14,179	HR 0.87 95% CI 0.70−1.09 14 trials. n=2,967	HR 0.86 95% CI 0.67−1.11 14 trials. N=2,967

Key: CI, confidence interval; df, degrees of freedom; het, heterogeneity; RR, relative risk
Notes: The number of trials includes multiple experimental arms for some studies **(a)** fixed effects (Mantel-Haenzel); **(b)** random effects (Der-Simonian Laird);), haematological response was defined as the proportion of participants with an increase in Hb concentration of 2 g/dl or more, or as an increase in haematocrit of six percentage points or more; **(c)** 16 studies; however, two studies split into subsets thus 18 trials included in meta-analysis

Source: assessment report (table 22, page 125)

Adverse events

4.15 The Assessment Group conducted meta-analyses (using data from the 2012 Cochrane review by Tonia et al.) to addresses whether, and to what degree, treatment with ESA 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 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 ESA. ESA therapy 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

4.16 The Assessment Group presented results for the subgroups pre-specified in the appraisal protocol including people with any cancer receiving platinum-based chemotherapy, women with ovarian cancer receiving platinum-based chemotherapy, people receiving concomitant iron supplementation and people unable to receive blood transfusion. It stressed the uncertainty given the small number of studies for each subgroup and that the results were not adjusted for multiple testing.

4.17 Comparing the effectiveness of ESA in people with any cancer receiving platinum-based chemotherapy (5 studies, n=1119), with the overall population, response to ESA therapy was generally better in people receiving platinum-based chemotherapy. However, the mean change in haemoglobin concentration was lower than that reported for the overall population, although not statistically significant. Therapy with ESA improved overall survival compared with no ESA therapy in people receiving platinum-based chemotherapy (HR 0.67, 95% CI 0.46 to 0.98); whereas ESA did not improve overall survival in the overall population. The risks of thromboembolic events and hypertension were also lower in people receiving platinum-based chemotherapy than in the overall population.

4.18 The Assessment Group reported 1 study by Ten Bokkel (1998) evaluating the use of ESAs in women with ovarian cancer (n=122), all of whom received platinum-based chemotherapy. ESA therapy compared with no ESA therapy improved anaemia-related outcomes, but increased the risk of thromboembolic events (RR 3.70, 95% CI 0.18 to 74.51). The study did not measure overall survival.

4.19 The Assessment Group identified 16 trials that evaluated the use of ESAs alongside iron supplementation, but commented that interpreting the results was hindered by the variety of types of supplements (in terms of

dosage, concentration of haemoglobin which triggers treatment, and administration route) and limited reporting in the publications.

4.20 The Assessment Group did not identify any trials that evaluated the use of ESAs in people unable or unwilling to receive blood transfusions. However, it stated that it was reasonable to assume that ESAs improve haemoglobin concentrations in people unable or unwilling to receive blood transfusion.

4.21 The Assessment Group conducted a post-hoc analysis of a subgroup of patients with a haemoglobin concentration of 11 g/dl or less at the start of treatment (14 trials) and in whom clinicians chose target haemoglobin of 13 g/dl or less (2 trials); the Assessment Group considered these patients to reflect the marketing authorisation of the ESAs. For the anaemia-related outcomes, the effectiveness of ESAs when evaluated in clinical scenarios closer to their licence was consistent with the results for the overall population included in the review. The analysis, which was subject to uncertainty (see section 4.16), also showed that the risk of mortality does not differ when ESAs in comparison with no ESA are used in clinical scenarios closer to their licence (inclusion concentration of 11 g/dl or less [HR 0.91, 95% CI 0.70 to 1.20]; inclusion concentration of 11 g/dl and target concentration of 13 g/dl or less [HR 0.50, 95% CI 0.20 to 1.23]) compared with overall populations included in the studies.

Health-related quality of life

4.22 Thirteen RCTS were included in the Assessment's Group's review of health-related quality of life. The Assessment Group reported a difference in (FACT-F) scores (functional assessment of cancer therapy-fatigue) in favour of ESA therapy compared with no ESA therapy (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. However, the Assessment Group stated that the study by Cella et al. (2002)

defined the threshold of a clinically important difference in quality of life as a mean difference of 3.0. For the FACT-general (G) and FACT-anaemia (An) outcomes, only 3 studies were included and the meta-analyses 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]). The Assessment Group stated that the results for health-related quality of life results should be interpreted with caution.

5 Comments from other consultees

5.1 Clinical specialists commented that ESAs correct anaemia, reduce the need for blood transfusion and improve quality of life; however their effect on life expectancy remains uncertain. They stated that although correcting anaemia improves patients' sense of well-being, their quality of life may not return to normal because they have cancer and are still receiving chemotherapy. Clinicians noted that side effects such as hypertension and thrombotic problems occur more commonly in ESA treated patients.

5.2 Clinical specialists noted that the American Society of Haematology and American Society of Oncology published guidelines in 2010 recommending the use the minimum dosages of ESA when a patient's haemoglobin concentration is less than 10 g/dl to avoid blood transfusion. Guidelines have been published by the National Comprehensive Cancer Network, restricting the use of ESA to patients with potentially curable malignancies, such as Hodgkin's lymphoma.

5.3 Patient experts commented that patients with symptomatic anaemia report varying levels of fatigue, breathlessness, weakness and inability to carry out everyday tasks. They emphasised their belief that ESA therapy improves outcomes related to cancer treatment per se and patients' quality of life. Patient experts noted

that although blood transfusion may improve anaemia more rapidly than ESAs, the effect of ESA treatment lasts longer. In addition, patients can now better access ESA treatment because of the availability of generics and biosimilars and the provision of ESAs through home delivery schemes. Patient experts stated that the advantages of treatment outweigh the increase in the risk of thrombotic events with ESA therapy.

6 Cost-effectiveness evidence

6.1 The Assessment Group identified 10 existing cost-utility studies. It noted that starting doses of ESA in the studies generally reflected the licensed doses, although the concentration of haemoglobin at which a clinician would offer treatment, and the target haemoglobin concentration varied between the studies and in some cases, were not reported. The Assessment Group stated that the more recent studies estimated quality of life as a function of haemoglobin concentrations.

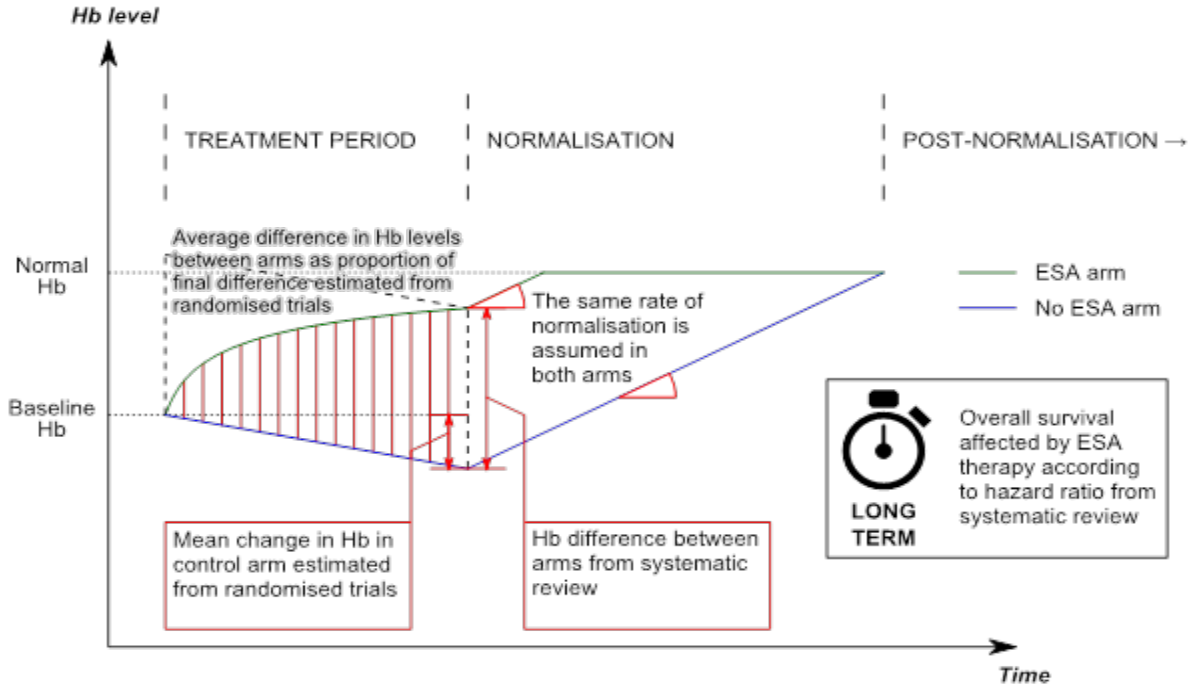
6.2 The analyses by Wilson et al. (2007) and Martin et al. (2003) were performed from a UK health service perspective and the resulting incremental cost effectiveness ratios (ICERs) were £150,000 and £8851 per QALY gained respectively. However, the study by Martin et al. (2003) was based on a subgroup of patients with stage IV breast cancer, in whom the authors assumed an increase in survival that was not statistically significant. The Assessment Group stated that this subgroup was identified post-hoc and that the trial underpinning the Martin et al. (2003) study was not powered to detect survival differences. The only other study that reported a favorable result (Borg et al. [2008] with an of ICER of €24,700 per QALY gained) did not assume that patients treated with ESA lived longer than those not treated with ESA; however the modeled patients discontinued ESA earlier than patients in the clinical trial underpinning the study.

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

Assessment Group's cost-effectiveness analysis

6.4 The Assessment Group developed a simple empirical model to assess the cost effectiveness of ESA therapy compared with non-ESA therapy. The model had 2 arms (treatment with or without ESAs) and 2 components; the short-term component (evaluating short-term costs and QALYs during treatment and during the time the haemoglobin returned to normal concentrations) and the long-term component (evaluating long-term QALYs after normalisation of haemoglobin, but not long term costs). The Assessment Group modeled short-term QALYs as changes in haemoglobin concentrations over time observed in the clinical trials, whereas it modeled 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 life-time 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 modeled patients was 59.1 years with a mean weight of 66.6 kg taken from the Assessment Group's systematic review of clinical effectiveness.

Figure 1 Model assumptions about haemoglobin concentration by model stage



Source: assessment report (figure 29, page 249)

6.5 The Assessment Group estimated the magnitude of the effectiveness of ESA compared with not using ESA from trials reporting intention-to-treat (ITT) analyses. The Assessment Group assumed that all ESAs are equally effective. 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 the non-ESA arm and mean number of red blood cell units transfused in the non-ESA arm, the Assessment Group calculated the weighted averages from the control arms of the studies included in the respective meta-analyses. The Assessment Group estimated patients' baseline haemoglobin concentration as 10.38 g/dl based on the weighted average of the studies included in its review. Because it assumed that haemoglobin

levels improved gradually in the ESA arm, the Assessment Group used the entire period of treatment to estimate the mean difference in haemoglobin concentration between treatment arms. The Assessment Group then applied the resulting mean difference as a proportion of the difference at the end of trial, resulting in a value of 80.6%.

6.6 The Assessment Group assumed a ‘normalisation period’ in the model, when haemoglobin concentrations increase at a constant rate until they reach normal concentrations. The Assessment Group assumed the same rate for both treatment arms, 0.2 g/dl per week, based on the opinion from clinical experts. The Assessment Group commented that this value was consistent with the rates of normalisation used in previous cost-utility studies.

6.7 To extrapolate overall survival in patients treated with, or not treated with, ESAs in its base-case, the Assessment Group first modeled survival in the control arm and chose an exponential distribution based on the weighted geometric average of the overall survival rate observed in the control arms of the included trials. The Assessment Group then derived a hazard ratio from its meta-analysis to estimate survival in the treatment arm. The Assessment Group estimated a mean overall survival of 2.67 years for the non-ESA arm and 2.76 years for the treatment arm. It also explored alternative scenarios.

6.8 To estimate the short-term QALY gains in the model, the Assessment Group modelled utility as a function of haemoglobin concentration, using utility values from the study by Harrow et al. (2011), in which SF-6D utility values were measured in 13,433 women with cancer and valued by the US general public using the standard gamble technique. The Assessment Group highlighted that the patient population in the study included only women with cancer who were not receiving ESAs and who may not necessarily

be receiving chemotherapy. The Assessment Group mapped the SF-6D values to EQ-5D values using regression analyses. 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 unit increase of 1 g/dl in haemoglobin concentration. The Assessment Group did not assign specific utility values to each haemoglobin concentration; instead it applied the utility increase of 0.028 per unit increase in haemoglobin until the end of 'normalisation' and adjusted for mean difference in haemoglobin concentrations between the treatment arms. The Assessment Group highlighted that the observational design of the study by Harrow et al. (2011) increased the risk of bias in the results due to potential unmeasured confounding variables.

6.9 For the long-term component of the model, that is, after stopping treatment with ESA and after a patient's haemoglobin has normalised, the Assessment Group estimated a constant utility value of 0.76 for both treatment arms from Tengs and Wallace (2000) and applying the age-related utility calculated from Ara and Brazier (2010). The Assessment Group stated that the estimated utility was highly uncertain because of lack of data and that the uncertainty could potentially have a large impact on the overall QALYs accrued in the analysis. The Assessment Group did not include disutilites associated with adverse events in its calculation of QALY because adverse events data in the included studies were not clearly defined and reported. However, the Assessment Group stated that including disutilites associated with adverse events could increase the ICERs given that most adverse events occurred more frequently in the ESA arm than in the non-ESA arm (see section 4.15).

6.10 The Assessment Group used the list price of each ESA per 1000 units from the BNF 66: 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 mean weekly dose, the Assessment Group combined into a single model parameter the rate of withdrawal from ESA, the rate of dose increases, and the rate of dose reductions estimated from the studies included in its review of clinical effectiveness and it used an average 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, 22,859 units and 141.1 micrograms for NeoRecormon, Eporatio and Aranesp respectively. The Assessment Group assumed that the duration of ESA treatment was 12 weeks in the model because most of the studies in the meta-analysis (13 of 23) reported a 12-week treatment period. The Assessment Group assumed that drug wastage would be minimal because of the wide variety of vial sizes for the ESAs; therefore, it did not account for drug wastage in the analysis.

6.11 Based on opinion of clinical experts, the average cost per administration of ESA used in the model was £8.16, 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%), a hospital staff nurse (16.3%) and self-administration (40.6%). The Assessment Group highlighted that the cost of administration may be slightly exaggerated because the Assessment Group calculated duration of treatment based on an intention-to-treat analyses from the trials. In the base case analysis, the Assessment Group assumed that patients would administer all ESAs once a week (based on the dosing schedule in the marketing authorisations and the included trials) for the entire 12 weeks treatment duration. The Assessment Group did not model any additional ESA use during the normalisation period, although it

noted that it was possible for people to continue ESA treatment up to four weeks after chemotherapy.

6.12 The unit cost for the supply of red blood cell was taken from the NHS blood and transplant and inflated to 2014/15 prices. In the absence of more recent data, the Assessment Group derived the cost of a transfusion appointment from the published study by Varney and Guest (2003). The Assessment Group assumed that ESA and non-ESA groups are equally likely to require iron supplementation; therefore it was not include it in the analysis.

6.13 The Assessment Group assumed a patient would get blood tests regularly during the chemotherapy period whether or not the patient was treated for anaemia, and that people using ESA would receive 4 additional blood tests post-chemotherapy. The cost for the additional blood tests was estimated from the PSSRU and NHS reference costs. The Assessment Group obtained resource use for adverse events by pooling the studies included in the review of the clinical effectiveness. The Assessment Group obtained the costs of treating adverse events (thromboembolic events, hypertension and thrombocytopenia) from the NHS reference costs. The Assessment Group assumed that patients in the model would experience at most one adverse event of each type. The Assessment Group assumed that the dosing schedule, administration cost, cost of red blood cell transfusion, additional blood tests and adverse events were similar for all the ESAs.

Table 5 summary of costs in the economic model

Cost Parameter	Value
Cost of drug therapy – No ESA	£0
Cost of drug therapy – Eprex, unit cost (Total cost)	£5.53 (£1641)
Cost of drug therapy – Binocrit, unit cost (Total cost)	£5.09 (£1510)
Cost of drug therapy – NeoRecormon, unit cost (Total cost)	£7.01 (£2611)
Cost of drug therapy – Eporatio, unit cost (Total cost)	£5.99 (£1643)
Cost of drug therapy – Retacrit, unit cost (Total cost)	£5.66 (£1678)
Cost of drug therapy – Aranesp*, unit cost (Total cost)	£1.47 (£2485)
Administration cost – No ESA	£0
Administration cost – ESA**	£98
Red blood cell transfusion cost – No ESA	£799
Red blood cell transfusion cost – ESA**	£467
Cost of additional blood test – No ESA	£0
Cost of additional blood test – ESA**	£60
Cost of treating adverse events – No ESA	£113
Cost of treating adverse events – ESA**	£148
Notes: * Darbepoetin (Aranesp) is measured in micrograms, whereas the epoetins are measured in international units ** Costs of ESA administration, red blood cell transfusion, additional blood test and adverse events are the same across all ESAs.	

Source: assessment report (table 74, page 301 and table 81, page 315)

Base-case results

6.14 The base-case analysis resulted in ICERs ranging from £19,429 per QALY gained for Binocrit to £35,018 per QALY gained for NeoRecormon compared with non-ESA treatment. The incremental costs of the ESAs compared with no ESA ranged from £1371 for Binocrit to £2472 for NeoRecormon, whereas the incremental QALY gain was 0.706 for all ESAs compared with no ESA. When the ICERs were translated to incremental net health benefits, the Assessment Group reported that 4 of the 6 ESAs showed slight net health benefits compared with no ESA treatment at a threshold of £30,000 per QALY gained. However at a threshold of £20,000 per QALY gained, only 1 ESA (Binocrit) showed a net health benefit compared with no ESA treatment.

6.15 The Assessment Group assumed that patients treated with ESAs avoid costs of £332 for red blood cell transfusions compared with patients not treated with ESA, but that this was outweighed by additional costs accrued in each ESA arm (including cost of drugs, drug administration, adverse events and additional blood tests). The Assessment Group noted that more than three-quarters of the total QALY gain associated with ESA use compared with not using ESAs (0.0706) accrued in the long-term component of the model (0.0582) compared with the short-term component (0.0124). This, according to the Assessment Group, demonstrates the importance of assuming that using ESA prolongs survival. The Assessment Group observed that the estimated short-term QALY gain of 0.0124 was lower than those reported in other analyses of cost effectiveness such as the review by Wilson et al. (2007), which reported a short-term QALY gain of 0.030.

Table 6 Summary of the base-case results

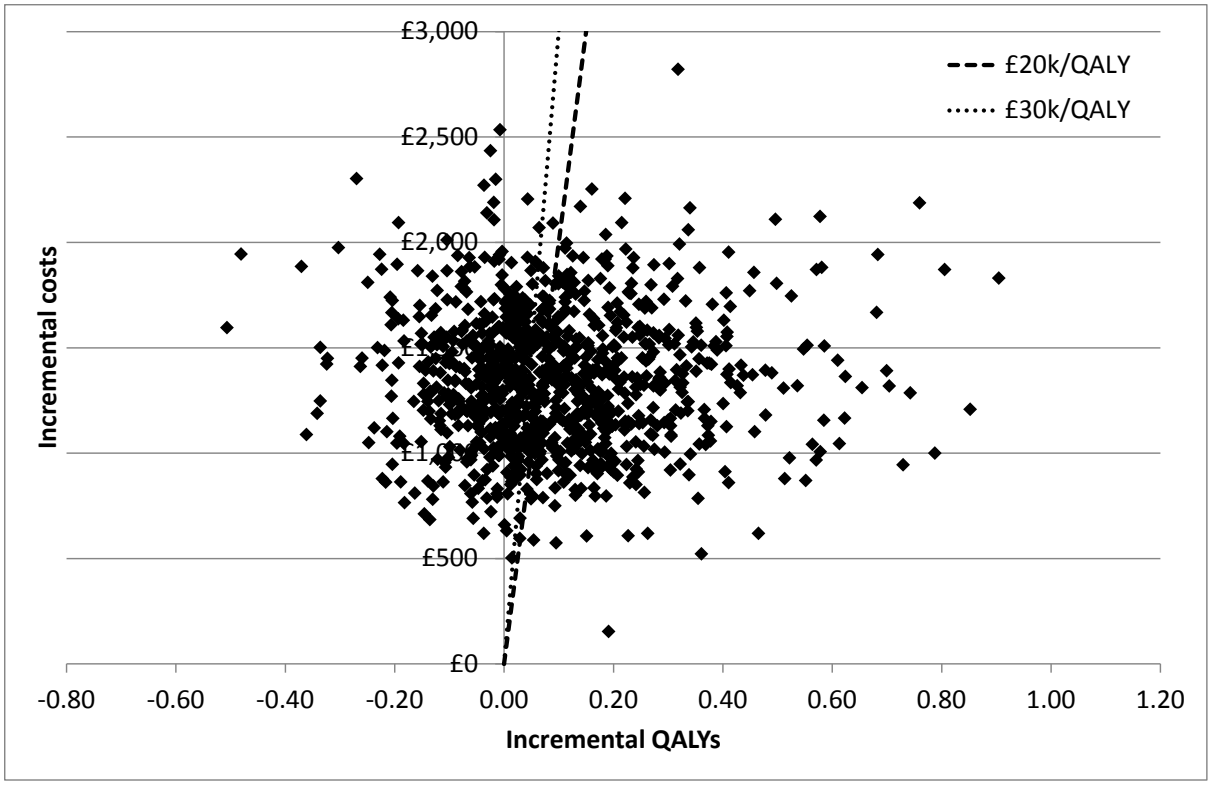
Treatment arm	No ESA	Epoetin alfa		Epoetin beta	Epoetin theta	Epoetin zeta	Darbe alfa
	–	Eprex®	Binocrit®	NeoRecormon®	Eporatio®	Retacrit®	Aranesp®
Total costs per strategy	£912	£2,414	£2,283	£3,384	£2,416	£2,451	£3,258
Total incremental costs vs. no ESA	–	£1,502	£1,371	£2,472	£1,504	£1,539	£2,346
Total discounted QALYs gained vs. no ESA	–	0.0706	0.0706	0.0706	0.0706	0.0706	0.0706
ICER vs. no ESA (£/QALY)	–	£21,279	£19,429	£35,018	£21,309	£21,804	£33,233
ICER (£/QALY)	–	Dominated by Binocrit® (Sandoz Ltd)	£19,429	Dominated by Binocrit® (Sandoz Ltd)	Dominated by Binocrit® (Sandoz Ltd)	Dominated by Binocrit® (Sandoz Ltd)	Dominated by Binocrit® (Sandoz Ltd)
INHB vs. no ESA at £20,000/QALY threshold	–	-0.005	0.002	-0.053	-0.005	-0.006	-0.047
INHB vs. no ESA at £30,000/QALY threshold	–	0.021	0.025	-0.012	0.020	0.019	-0.008

Key: Darbe alfa, darbepoetin alfa; ESA, erythropoiesis stimulating agents; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; QALYs, quality-adjusted life years; vs, versus;

Source: assessment report (table 80, page 313)

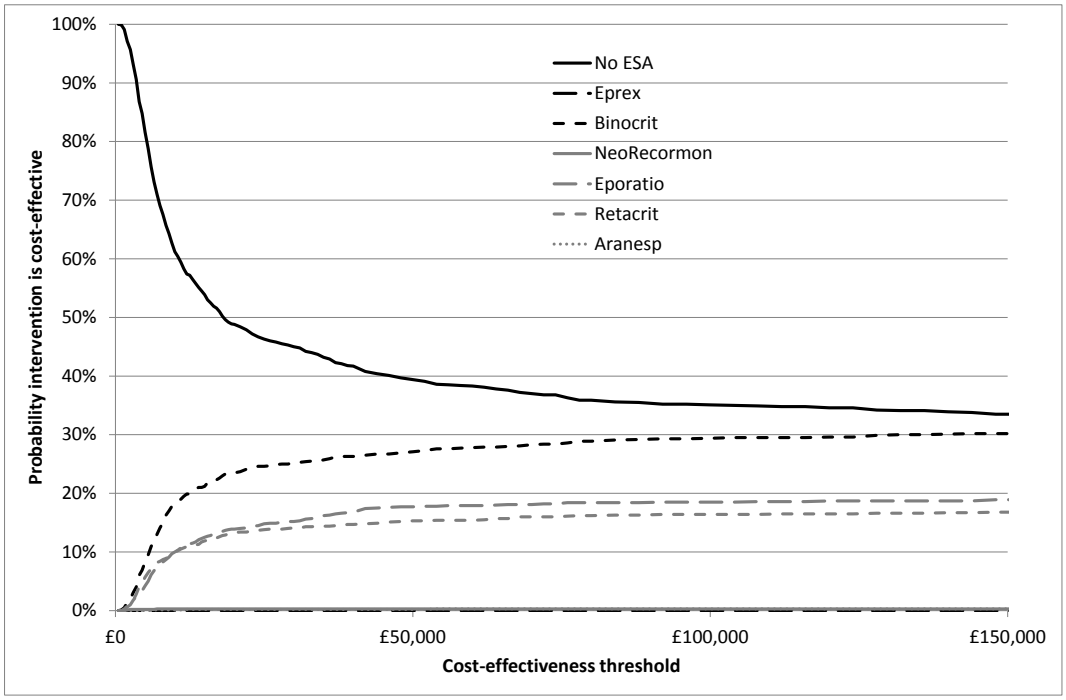
6.16 In the Assessment Group's probabilistic analysis, the ICERs ranged from £14,724 per QALY gained for Binocrit to £27, 226 per QALY gained for NeoRecormon. The 95% credible intervals covered a range of £2,322 per QALY gained to dominated, that is, the ESAs having higher costs and lower QALYs than 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, while the other ESAs had less than 20% chance of being cost-effective. For the ESA with the lowest acquisition cost (Binocrit), the Assessment Group reported that all the simulations fell into the north-west and north-east quadrants of the scatterplot. In addition, it stated that 31.4% of the simulations fell into the north-west quadrant, suggesting that the ESAs may reduce QALYs while at higher costs compared with not using ESAs.

Figure 2 Base-case scatterplots for Binocrit



Source: assessment report (figure 47, page 320)

Figure 3 Cost effectiveness acceptability curves



Source: assessment report (figure 48, page 322)

Scenario analyses

6.17 The Assessment Group explored a scenario where patients using ESAs lived no longer or shorter 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 shot-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 Assessment Group performed a threshold analysis of the costs of ESAs, and showed that the weekly cost of the ESAs would need to decrease to £32 from the base-case value of £137 (for Binocrit) for the ESAs to be considered cost-effective at a threshold of £20,000 per QALY gained. The probabilistic sensitivity analysis resulted in ICERs ranging from £96,754 per QALY gained for Binocrit to £174,193 per QALY gained for NeoRecormon.

6.18 In a second scenario analysis, rather than using BNF prices, the Assessment Group applied the best wholesale acquisition prices available for the ESAs to its base-case analysis. The wholesale prices reflect the

actual prices paid by the NHS for ESAs, and these are designated commercial in confidence. The results show a substantial reduction in the ICERs: deterministic ICERs ranging from [redacted] per QALY gained for Retacrit (with the lowest wholesale price) to [redacted] for Aranesp (with the highest wholesale price) and probabilistic ICERs ranging from [redacted] for Retacrit to [redacted] per QALY gained for Aranesp. The Assessment Group reported that the 95% credible intervals ranged from a value showing that the ESAs dominate non-ESAs (in 5% of simulations) to the opposite, that is, non-ESAs dominate ESA (in 26.4% of simulations). The Assessment Group also stated that the results of probabilistic analyses of incremental net health benefits indicated overlapping 95% confidence intervals for all ESAs, suggesting that the cost-effectiveness of the ESAs are similar.

6.19 When the Assessment Group combined these two scenarios analyses and applied the wholesale prices to the scenario where people using ESAs do not live any longer than patients not using ICERs, the ICERs ranged from (Retacrit to Aranesp): [redacted] per QALY gained in the deterministic analysis and [redacted] per QALY gained in the probabilistic analysis. The probability that Retacrit would be cost-effective at a threshold of £20,000 per QALY was above 50%. The Assessment Groups noted that the price at which the NHS buys ESAs and whether or not one assumes that use of ESAs keep people alive longer were the most important drivers of the cost-effectiveness results.

6.20 The Assessment Group performed a scenario analysis using only trials where the initial haemoglobin concentration of patients was 11 g/dl or less, that is, closer to the ESA marketing authorisation. The Assessment Group based most clinical parameters including overall survival on the included trials for this subgroup only, whereas it used 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 ESAs. At £20,000 and £30,000 per QALY gained, treatment without ESA had a greater probability of being cost effective than any of the individual ESAs.

Overall survival scenario analyses

6.21 The Assessment Group performed 3 scenario analyses exploring the assumptions regarding overall survival, using the base-case drug prices. In the first scenario, the Assessment Group assumed that treatment with EPO improves survival (as estimated by the hazard ratio from the base case) but for the first 3 years only, after which the rate of mortality was equal for both treatment arms. This resulted in an ICER range of £42,584 per QALY gained for Binocrit to £76,751 per QALY gained for NeoRecormon. The incremental long-term QALYs and incremental total QALYs were 0.0198 and 0.0322 compared with the base case-estimates of 0.0582 and 0.0706 respectively. 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 accrued over the first 3 years after treatment with ESA. The probabilistic ICERs ranged from £39,836 to £71,589 per QALY gained.

6.22 In the second scenario varying assumptions about overall survival, the Assessment Group fitted a Weibull distribution with proportional hazards to the control arm of a single study (Untch et al. (2011)), which it considered provided a better fit for this study than did the exponential distribution. However, the Assessment Group assumed the same overall survival gain for ESA treatment as in the base case. The ICERs for the ESAs ranged from £14,726 to £26,541 per QALY gained in the deterministic analysis and from £12,649 to 22,516 per QALY gained in the probabilistic analysis.

6.23 In the third overall survival scenario, the Assessment Group modeled overall survival based on the study by Littlewood et al. (2011), because none of the proportional hazards models tested (exponential and Weibull) provided an accurate fit to the data from Littlewood et al. The Assessment Group instead fitted a log-normal distribution, which does not assume proportional hazards, to the Kaplan-Meier curves for the two treatment arms of the study. The resulting ICERs for the ESAs compared to treatments not including ESAs ranged from £4271 to £7698 per QALY gained. The Assessment Group did not present probabilistic sensitivity analysis for this scenario because it did not quantify the uncertainty in the fitting of the log-normal distributions.

Table 7 Summary of deterministic ICERs compared with no ESAs for the different scenarios

Scenario	Eprex	Binocrit	NeoRecormon	Eporatio	Retacrit	Aranesp
Base case	£21,279	£19,429	£35,018	£21,309	£21,804	£33,233
No OS gain	£120,995	£110,477	£199,118	£121,166	£123,983	£188,968
Wholesale drug prices + base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wholesale drug prices + no OS gain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subgroup with initial Hb concentration of 11 g/dl or less	£13,849	£12,593	£23,013	£13,826	£14,206	£21,785
OS gain – 3 years only	£46,638	£42,584	£76,751	£46,704	£47,790	£72,839
Weibull curve for OS (Untch et al. [2011])	£16,128	£14,726	£26,541	£16,150	£16,526	£25,188
Log-normal curve for OS (Littlewood et al. [2011])	£4,678	£4,271	£7,698	£4,684	£4,793	£7,306

Hb – haemoglobin, OS – overall survival

Univariate sensitivity analyses

6.24 The Assessment Group performed various univariate (one-way) sensitivity analyses around the base-case ICERs. For the utility associated with increasing haemoglobin concentrations, the Assessment Group assumed alternate values of 0.009 (SF-6D value from Harrow et al. [2011]) and 0.016 (EQ-5D value for anaemia related to chronic kidney disease). This increased the base case ICERs by a minimum of £1600 and £2600 for Binocrit and up to £2800 and £4700 for NeoRecormon, using the values of 0.016 and 0.009 respectively. However, applying a higher utility value of 0.06 used in the review by Wilson et al. (2007) decreased the base-case ICERs to below £20,000 per QALY gained for all ESAs except for NeoRecormon and Aranesp, which had ICERs of £29,157 per QALY gained and £27, 671 per QALY gained respectively compared with treatments not including ESAs. When long-term costs of £20,000 per year associated with on-going cancer treatment (such as costs of maintenance therapy, subsequent chemotherapy cycles or relapse) were included in the model, 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 2) generally increased the ICERs slightly. All other scenarios had minimal impact 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 blood transfusion appointment and the cost of adverse events.

6.25 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 TA142 by Wilson et al. (2007) (£150,342 per QALY gained). In attempting to explore these differences, the Assessment Group adjusted its model to incorporate some parameters used in TA142. 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 updated parameters that had the most impact on 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. (2007)
- lower unit costs and dosing schedule associated with ESAs

7 Equality issues

7.1 Consultees raised the potential equality issue regarding people unable to receive blood transfusion for religious reasons (e.g. Jehovah's Witnesses). The Committee took this issue into account when developing TA142, and 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 with cancer treatment-related anaemia that is likely to have an impact on their survival.

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Appendix A: Supporting evidence

Related NICE guidance

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

Appendix B: Clinical efficacy section of the draft European public assessment report

Epoetin alfa

Scientific discussion – initial marketing authorisation

Assessment report – after initial authorisation

Epoetin beta

Scientific discussion – initial marketing authorisation

Scientific discussion – after initial authorisation

Epoetin theta

Assessment report – initial marketing authorisation

Epoetin zeta

Scientific discussion – initial marketing authorisation

Assessment report – after initial authorisation

Darbepoetin alfa

Scientific discussion – initial marketing authorisation

Scientific discussion – after initial authorisation